Development of Palladium-Catalyzed and Iodine-Mediated Formal [4+1] Annulation Protocols.
Progress toward a New Fulvene-Based Organocatalytic Platform for Carbonyl α-Functionalization.

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Submitted in partial fulfillment of the

requirements for the degree

of Doctor of Philosophy

in the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2011

ABSTRACT

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The development of a new palladium-catalyzed [4+1] annulation protocol is described. This process involves an oxidative palladium-catalyzed intramolecular vinylcyclopropanation of dienyl β-ketoesters followed by a magnesium iodide-mediated vinylcyclopropane-cyclopentene rearrangement. The cyclopropanation makes use of magnesium perchlorate to increase reactivity at the α-carbon of the β-ketoesters. The protocol has been demonstrated to be effective in the annulation of a number of substituted dienyl β-ketoesters.

The development of a one-pot iodine-mediated Lewis acid-promoted [4+1] annulation protocol is described. The protocol utilizes an iodine-mediated vinylcyclopropanation of dienyl β-ketoesters followed by vinylcyclopropane-cyclopentene rearrangement. Magnesium perchlorate, used to promote the first reaction, and iodide are used to effect the vinylcyclopropane-cyclopentene rearrangement. The application of the protocol to a broad range of substituted dienyl β-ketoesters is described.

Progress toward a fulvene-based organocatalytic paradigm has been made. The diastereoselective α-allylation of a camphor-derived indenyl fulvene has been demonstrated. The reversible formation of fulvenes from carbonyls and electron deficient cyclopentadienes under mild nucleophilic amines catalysis has also been demonstrated and applied to several aryl and alkenyl aldehydes. Transfulvenation between benzaldehyde- and cinnamaldehyde-derived fulvenes has also been demonstrated.

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CHAPTER 1

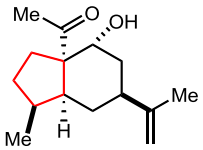
Development of a Formal [4+1] Cycloaddition: $Pd(OAc)_2$-Catalyzed Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters and MgI_2-Promoted Vinylcyclopropane-Cyclopentene Rearrangement[1]

Introduction

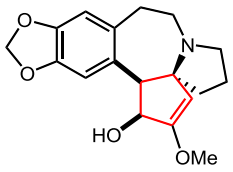
Improving our ability to access complex molecular architectures quickly and easily stands as an area continually worthy of investigation. Indeed, access to biologically relevant molecular structures has led to significant advancements in our capacity to treat countless diseases, syndromes, and injuries. Of the molecular architectures common to these life-saving treatments, the six-membered ring stands unambiguously as the most common. Synthetic organic chemistry has given us a number of tools to appropriately synthesize these six-membered ring containing compounds. For example, the Robinson annulations and the Diels-Alder reaction – both specifically used to synthesize six-membered cyclohexane rings – were pivotal in the rapid synthesis of cholesterol and a number of other related hormones.[2] The utility of these reactions can be measured by the quite literally thousands of instances of their use in the organic literature.

Five-membered rings are almost certainly the second most-common structural motif after to six-membered rings. These five-membered structures can be found in almost as many useful natural and unnatural compounds. In addition to being found along side six-membered rings in molecules like the aforementioned steroids, they are the major structural unit in prostaglandins and countless other natural product molecules (Figure 1). These structures, however, do not benefit from operationally facile and widely used organic transformations specific to the synthesis of five-membered rings. Instead, chemists must often utilize more traditional synthetic routes that often lead to particularly long and cumbersome syntheses.

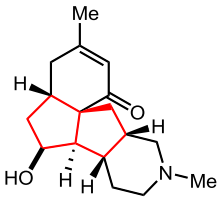
Figure 1. Natural products containing cyclopentane and cyclopentene ring systems.



alpiniol



cephalotaxine

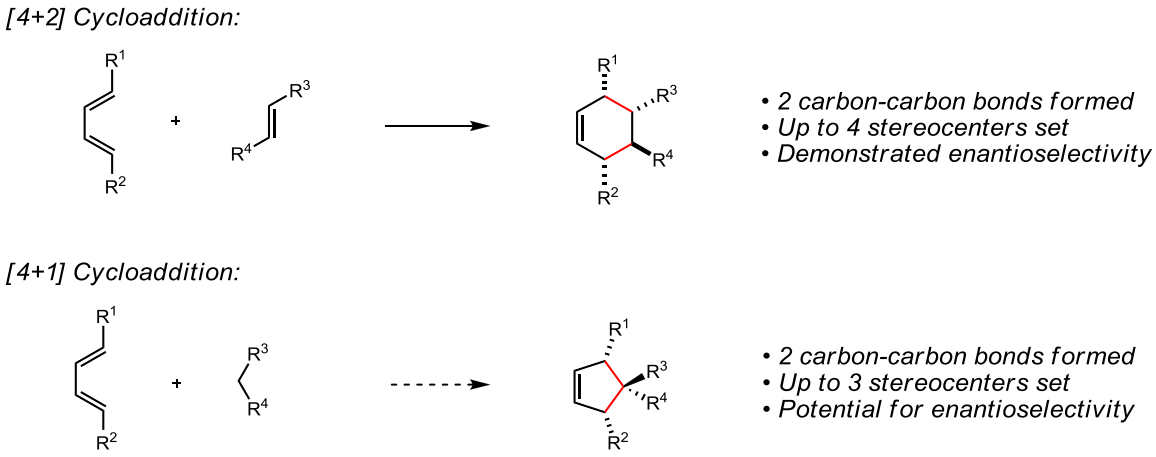


magellanine

Cycloadditions, such as the aforementioned Diels-Alder reaction, have been proven to be one of the most effective reaction classes in organic synthesis for the rapid generation of many organic ring systems.[3] The rapid generation of multiple carbon-carbon bonds along with the ability to set several stereogenic centers in one synthetic step is largely unrivaled by more traditional organic reactions. In addition, the use of chiral Lewis acid catalysis has enabled chemists to carry out the Diels-Alder with exceptional enantioselectivity. In light of the advantages of this reaction, a number of cycloadditions for other ring sizes, such as the [5+2][4], [2+2+2][5], and the [4+4][6] cycloadditions, have

been developed. Cycloadditions for the construction of five-membered rings, viz. the [4+1] cycloaddition, have received little attention, even given many the many advantages that parallel the [4+2] cycloaddition (Figure 2). Although several important [4+1] cycloadditions have been reported, many suffer from limitations in scope and practicality.[7] The development of a rapid, mild, and operationally facile [4+1] cycloaddition would greatly benefit those seeking to synthesize molecules containing the ubiquitous 5-membered ring. Accordingly, we aimed to develop an efficient and practical method for [4+1] cycloadditions for the construction of cyclopentene ring systems.

Figure 2. Comparison of demonstrated advantages of the [4+2] Diels-Alder reaction and potential advantages of a [4+1] cycloaddition.

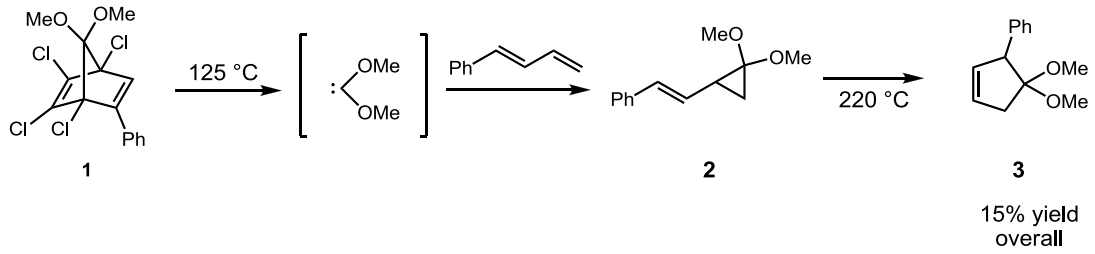


Previous Examples of the [4+1] Cycloaddition for the Synthesis of Cyclopentenes

The potential opportunity in developing an effective [4+1] cycloaddition has not been overlooked by the synthetic community and a number of formal [4+1] protocols have been developed. Most investigators have pursued the reaction paradigm by utilizing various carbene additions to dienes; often followed by a requisite vinylcyclopropane-cyclopentene (VCP-CP) rearrangement due to the propensity of carbenes to add in a 1,2-manner. Although many investigations have utilized more complicated diene structures such as vinylallenes,[8] diallenes,[9] and vinylketenes,[10] greatly limiting scope and practicality, a few investigations have successfully developed formal [4+1] cycloadditions with simple dienes. The most notable contributions are those of Hoffman,[11] Spino,[12] Hudlicky,[13] and Danheiser.[14]

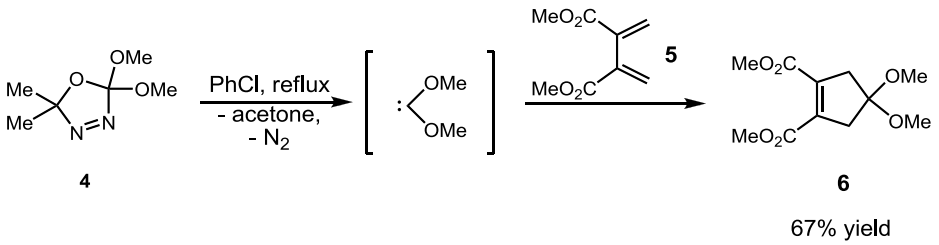
The first such example of a [4+1] cyclization was reported by Hoffmann and Lilienblum in 1977 (Figure 3).[11] In this seminal publication, the authors used the dimethoxycarbene precursor **1** that, in the presence of an appropriate diene, underwent a [2+1] cyclization to furnish the vinylcyclopropane **2**. At elevated temperatures the vinylcyclopropane isomerized to the desired formal [4+1] product **3**. Although the work was an important starting point in the development of an effective and practical [4+1] approach to cyclopentene products, the requisite phenyl and dimethoxy substitution, elevated temperatures, and poor overall yield prevented the wide adoption of the annulation protocol.

Figure 3. Hoffmann's formal [4+1] cycloaddition.



The dimethoxy carbene [4+1] paradigm was extended by work of Spino and coworkers (Figure 4).[12] In this investigation, the use of dimethoxycarbene precursor **4** led to the isolation of both 1,2- and 1,4-addition products. It was discovered that by utilizing dienes bearing electron withdrawing substitution, such as that of **5**, the [4+1] product **6** could be obtained directly without the need of a separate isomerization step. Later investigations suggested that the reaction was concerted, at least in cases where the diene exhibits substitution by electron withdrawing groups.[15]

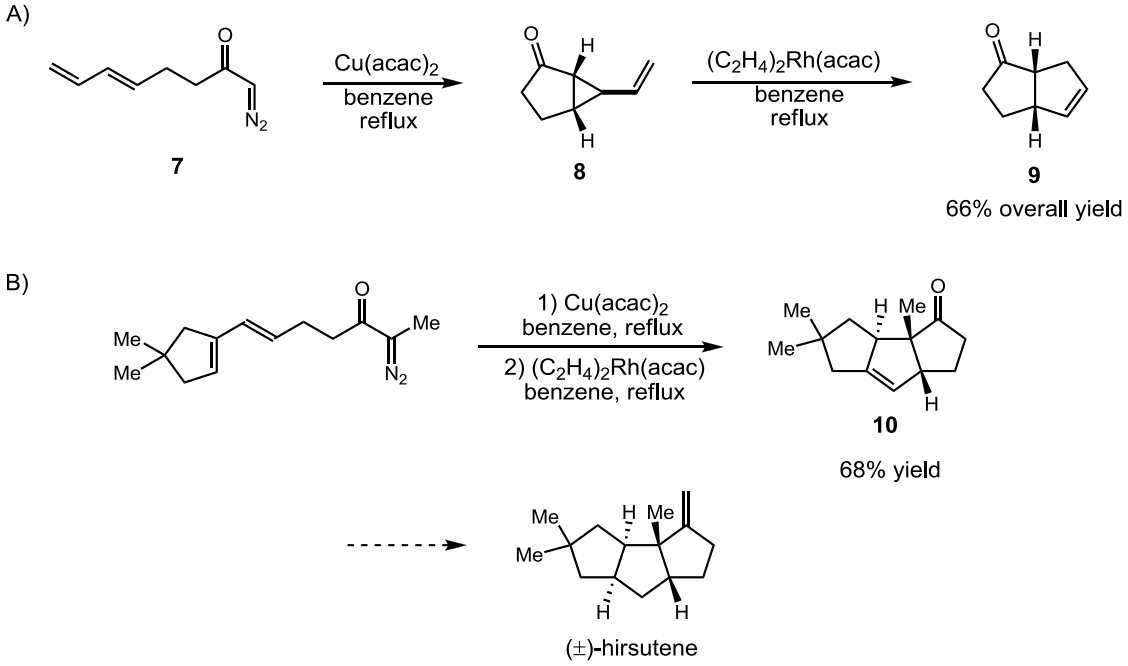
Figure 4. Spino's dimethoxycarbene initiated [4+1] cycloaddition.



An important advancement in the pursuit of a mild and practical [4+1] cycloaddition was developed by Hudlicky and coworkers in 1980.[13] In this investigation, the authors subjected diazoketones bearing pendant diene substitution, such as that of **7**,

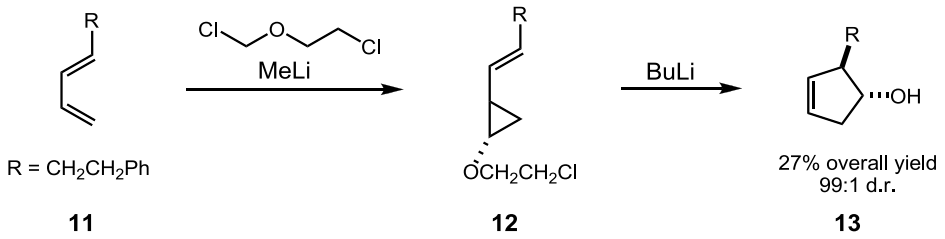
to $Cu(acac)_2$ in refluxing benzene to yield vinylcyclopropanes like **8** in good yield (Figure 5, A). The vinylcyclopropanes could then be isomerized to cyclopentene products like **9** using either pyrolysis or $(C_2H_4)_2Rh(acac)$ in refluxing benzene. The utility of the reaction protocol was demonstrated by the rapid generation of the polycyclic hirsutene natural product skeleton **10** and its formal total synthesis (Figure 5, B). In subsequent communications, Hudlicky and coworkers reported additional syntheses of isocomenic acid and epiisocomenic acid using their developed methodology.[16] While the advancement made the [4+1] cycloaddition significantly broader and more practical than its contemporaries, the reaction still suffered from the requirement to first form the requisite diazoketones.

Figure 5. A) Hudlicky's carbene addition/isomerization formal [4+1] annulation protocol and B) the group's reported formal total synthesis of (±)-hirsutene.



A protocol for the diastereoselective synthesis of cyclopentenyl alcohols was developed by Danheiser and coworkers utilizing a chloromethyl ether carbene precursor (Figure 6).[14] Under the described reaction conditions, chloromethyl chloroethyl ether was treated with methyllithium to generate the alkoxy carbene which underwent 1,2-addition to diene **11**. Upon treatment of the alkoxy-substituted vinylcyclopropane **12** with an excess of butyllithium the vinylcyclopropane alkoxide salt is formed. This salt then undergoes an alkoxy-accelerated 1,3-sigmatropic rearrangement to furnish the desired cyclopentene product **13**. While the reaction represents an interesting entry into stereospecific cyclopentenyl alcohols, the reaction conditions are intolerant to either base-sensitive or electrophilic substituents.

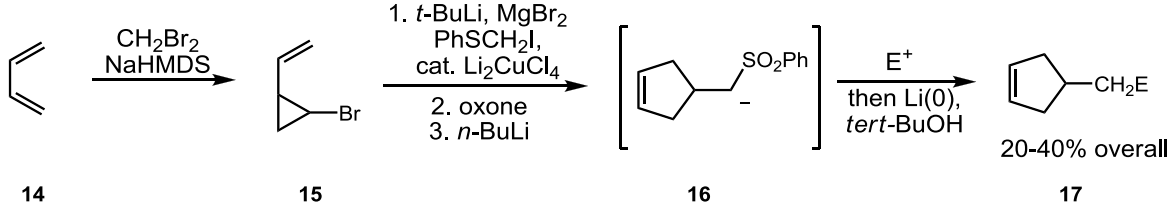
Figure 6. Danheiser's oxocarbene/oxyanion-promoted rearrangement formal [4+1] protocol.



The Danheiser group also investigated a more general [4+1] reaction protocol for the synthesis of alkyl substituted cyclopentenes (Figure 7).[17] In this reaction sequence, a carbene is produced upon treatment of dibromomethane with sodium hexamethyldisilazide. The bromocarbene then adds in a 1,2-fashion to diene substrate **14** to furnish bromovinylcyclopropane **15**. In a separate pot, the bromovinylcyclopropane undergoes lithium halogen exchange upon treatment with *tert*-butyllithium, which then

undergoes a nucleophilic addition to the phenyl iodomethyl thioether in the presence of catalytic Li_2CuCl_4. Oxidation of the thioether to the sulfone with oxone and subsequent α-deprotonation facilitates the anion-accelerated 1,3-sigmatropic rearrangement to furnish the cyclopentene anion intermediate **16**. Finally, upon treatment with an electrophile and desulfonation with lithium in *tert*-butanol, the substituted alkyl cyclopentene **17** is obtained. While perhaps the most general [4+1] annulation reaction to date, the cumbersome and lengthy reaction protocol suffers from low overall yield, relatively harsh reaction conditions, and poor functional group tolerance.

Figure 7. Danheiser's bromocarbene addition/carbanion accelerated 1,3-sigmatropic rearrangement form [4+1] annulation protocol.



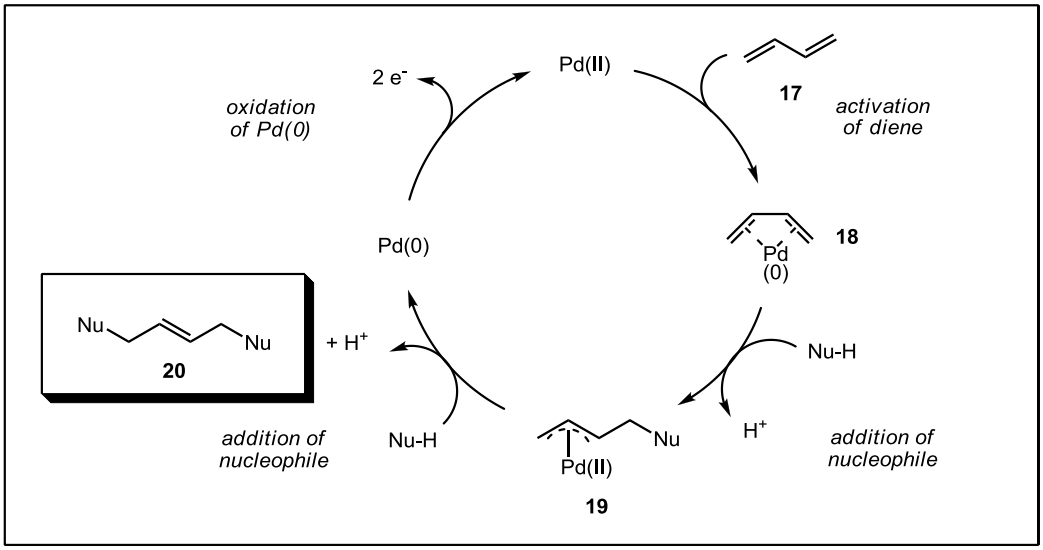
Although many interesting examples of formal [4+1] cycloadditions have been developed, none have become practical solutions to synthetic problems. Given the ubiquity of cyclopentane rings in natural products and other biologically relevant molecules, the potential for a mild and practical [4+1] is still tremendous. Indeed, as advancements in general synthesis technology develop further, our inadequacies in this very important reaction class are becoming even more apparent. For these reasons we sought to realize a mild, efficient, and general approach to the synthesis of cyclopentene containing molecules through a [4+1] reaction protocol.

Palladium Catalyzed 1,4-Activation of 1,3-Dienes

Palladium(II) salts have long been known to catalyze the 1,4-activation of 1,3-dienes which the Bäckvall group has exploited using a number of heteroatom and carbon nucleophiles.[18] The oxidative reaction pathway, in which the substrate is formally oxidized utilizing some terminal oxidant, was especially interesting as it could catalyze the addition of two nucleophiles to the 1- and 4-positions of a simple diene. This reaction paradigm quickly caught our attention for its potential in a hypothetical [4+1] cycloaddition due to the generally mild reaction conditions, functional group tolerance, and ability to form carbon-carbon bonds from traditional carbon nucleophiles.

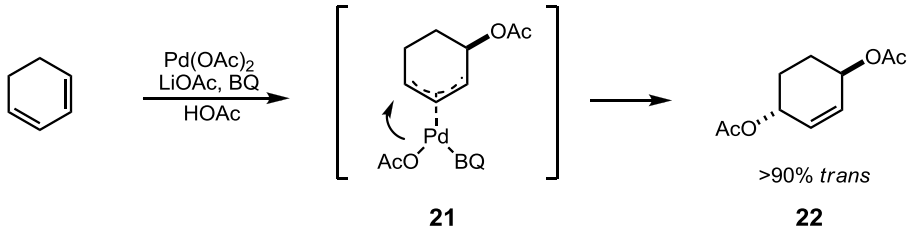
In the catalytic cycle of palladium-catalyzed 1,4-activation of 1,3-dienes (Figure 8), palladium first coordinates with the diene **17** – activating it for nucleophilic attack. A nucleophile then attacks the highly electrophilic palladium-diene complex **18**, generating a palladium-π-allyl intermediate **19**. The electrophilic π-allyl complex then undergoes attack by a second nucleophile to give the desired 1,4-activation product **20**. Palladium(II) is then regenerated from palladium(0) through the use of an external oxidant, starting the catalytic cycle over again.

Figure 8. Catalyst cycle for palladium-catalyzed 1,4-activation of 1,3-dienes.



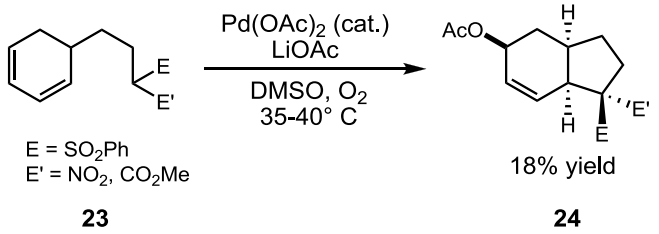
This reaction paradigm was originally discovered by Davidson in 1971 in which treatment of cyclohexadiene with acetic acid in the presence of $Pd(OAc)_2$ resulted in the formation of 1,4-acetoxy-2-cyclohexene.[19] At the time, the reaction was incorrectly identified as a radical chain mechanism. Subsequent work by Bäckvall and coworkers helped to elucidate the mechanism and diastereoselectivity of the reaction (Figure 9). Bäckvall's work showed that the first nucleophilic attack by acetate occurred from the opposite face of the palladium diene complex, while the second attack occurred via a migration of acetate from the palladium metal center of the π-allyl complex **21**. This mechanism resulted in the formation of the *trans*-1,4-diacetoxycyclohexene **22**.[20] The addition of LiCl caused the formation of the palladium chloride π-allyl species and the acetate nucleophile is therefore delivered externally, resulting in the *cis* product.

Figure 9. Bäckvall's investigation of palladium-catalyzed *trans*-1,4-acetoxylation of 1,3-cyclohexadiene.



The Bäckvall group later extended the methodology to carbon nucleophiles including allyl silanes[21] and allenes[22]. Perhaps most interesting, however, was the use of electron withdrawing group-substituted pendant carbon nucleophiles in the synthesis of complex hydroindene structures (Figure 10). In the reported reaction, the diene structure with a pendant activated carbon nucleophile **23**, underwent intramolecular nucleophilic attack to give a palladium π-allyl complex that was intercepted by an acetate nucleophile. This process led to the isolation of hydroindene product **24**. The reaction also utilized oxygen as the terminal oxidant, resulting in only water as the oxidation byproduct. Although the successful usage of simple carbon nucleophiles represented a significant advance for the palladium-catalyzed 1,4-activation paradigm, practicality was limited by particularly low isolated yields.

Figure 10. Activated carbon nucleophiles in the 1,4-activation of 1,3-cyclohexadiene.

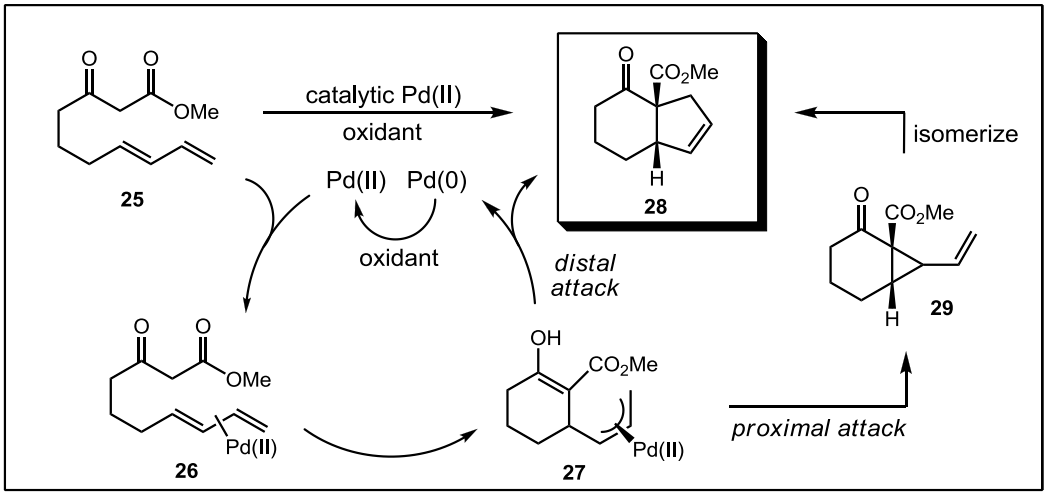


Although examples of the use of neutral activated carbon nucleophiles in the palladium-catalyzed 1,4-activation of 1,3-dienes are rare in the literature, we thought the former example provided important proof-of-concept that a palladium-catalyzed [4+1] annulation reaction was possible. If a single carbon nucleophile could be used for each of the two nucleophilic attack events, we reasoned, a mild and practical [4+1] reaction could be realized.

Proposed Reaction Design

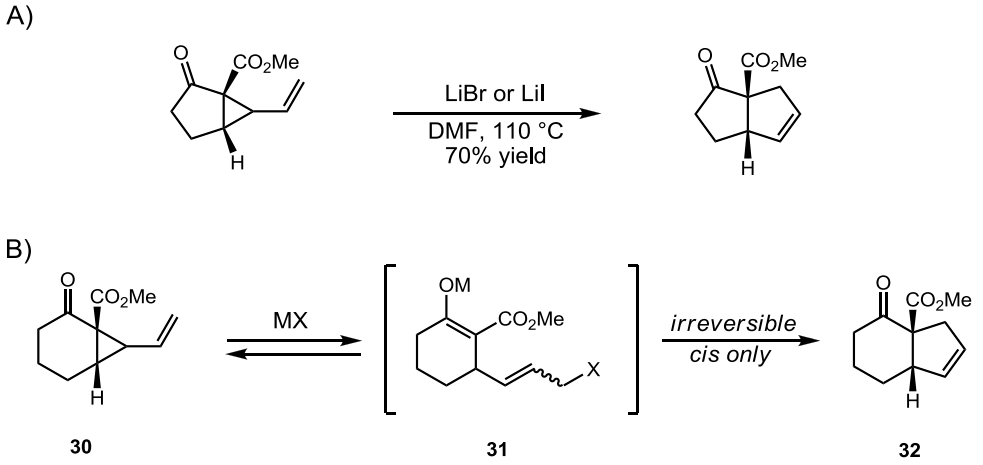
It is on the basis of Bäckvall's pioneering work that we envisioned a single activated carbon nucleophile for intramolecular 1,4-functionalization of a 1,3-diene to achieve a formal [4+1] cycloaddition (Figure 11). In our mechanistic design, palladium coordination of diene **25** would activate the substrate for intramolecular nucleophilic attack by the α-carbon of the β-ketoester, forming π-allyl palladium intermediate **27**. After tautomerization, the α-carbon could again serve as a nucleophile on either the proximal or distal terminus of the π-allyl palladium complex. Whereas distal attack would furnish the desired [4+1] product **28** directly, proximal attack would yield vinylcyclopropane **29** which could then be isomerized to the desired cyclopentene product via a VCP-CP rearrangement.

Figure 11. Proposed reaction scheme for a palladium catalyzed [4+1] annulation protocol.



Due to the propensity of carbene additions to 1,3-dienes to go through 1,2- rather than 1,4-mechanistic pathways, we envisioned the likelihood for distal attack to be particularly high. In addition to isomerization techniques developed by Hudlicky in his own [4+1] protocol[13], we envisioned mild isomerization techniques similar to those presented by Ikegami and coworkers in which vinylcyclopropanes were isomerized to cyclopentenes by treatment with LiI or LiBr (Figure 12, A).[23] In the envisioned VCP-CP rearrangement (Figure 12, B), a Lewis acid/nucleophilic counterion pair is used to open vinylcyclopropane **30** to the allyl iodide or allyl bromide intermediate **31**. The intermediate can then collapse either back to the vinylcyclopropane in an equilibrium fashion, or irreversibly form cyclopentene **32**. This method offers the potential advantages of very mild reaction conditions and low cost of the reagent salt.

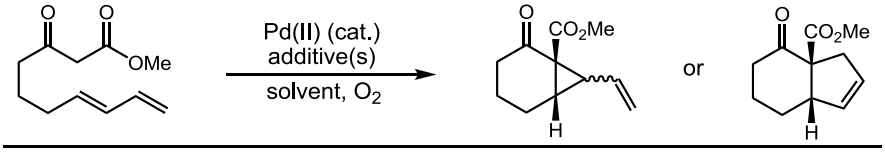
Figure 12. A) Ikegami's LiI promoted VCP-CP rearrangement, and B) reaction scheme for proposed VCP-CP rearrangement.



Results and Discussion

Our initial investigations towards realizing a formal [4+1] cycloaddition involved *β*-ketoester **1** and catalytic amounts of $Pd(OAc)_2$. Unfortunately, all reaction conditions previously described in the literature for similar reactions resulted in none of the desired vinylcyclopropane or cyclopentene products. The conditions previously utilized by Bäckvall to effect attack by activated carbon nucleophiles with and without additional acetate failed to convert the substrate (entries 1 & 2). Conditions similar to those developed by Stolz and coworkers for the annulation of indoles also failed (entry 3).[24] Worse yet, the *para*-benzoquinone oxidant used by Bäckvall was incompatible with our substrate as its addition resulted in exclusive formation of the Diels-Alder adduct between the diene and the electron-deficient olefin of *para*-benzoquinone (entry 4).

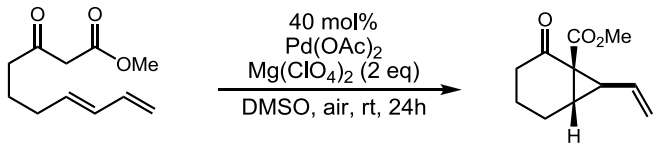
Table 1. Attempted palladium-catalyzed [4+1] annulation reactions under various known reaction conditions.



entry	Pd(II)	additive(s)	solvent	result
1	$Pd(OAc)_2$	LiOAc	DMSO	no rxn
2	$Pd(OAc)_2$	none	DMSO	no rxn
3	$Pd(OAc)_2$	pyridine	toluene	no rxn
4	$Pd(OAc)_2$	LiOAc, BQ	DMSO	D-A adduct

Work by Yang and coworkers for a similar reaction involving the attack of *β*-ketoamides onto simple olefins led us to believe that the presence of a Lewis acid may be necessary to facilitate the attack of the nucleophilic *β*-ketoester.[25] We hypothesized that the addition of Lewis acid would increase the amount of enol character – the active nucleophile in the reaction – and therefore allow the reaction to progress. In line with our hypothesis, the addition of $Mg(ClO_4)_2$ resulted in the isolation of a modest yield of the vinylcyclopropane (Figure 13). While the reaction yield was low, this was an important proof-of-concept and was the first example of a palladium-catalyzed bis-addition of a single carbon nucleophile to a 1,3-diene. The example also showed that the 1,2-addition was indeed preferred over the 1,4- and an additional isomerization step would be necessary.

Figure 13. The first example of a palladium-catalyzed vinylcyclopropanation.



15% yield

33

Attention was then turned to optimizing the yield of the newly discovered palladium-catalyzed cyclopropanation reaction. Oxidation of cyclohexanone to the corresponding cyclohexenone had previously been reported by Bierling in the presence of $PdCl_2$ and air and we sought to avoid the possibility of a similar oxidation of either the starting material or product under our aerobic oxidation conditions.[26] To do this, we subjected geminal-dimethyl substituted β-ketoester **34** to the reaction conditions (Figure 14). In agreement with our hypothesis, the yield of vinylcyclopropane **35** far exceeded that of previous reactions. The reaction, however, still appeared to lack turnover of the palladium catalyst as yields were limited by catalyst loading.

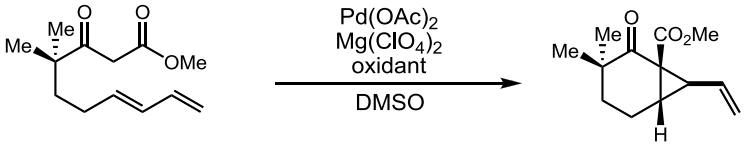
Figure 14. The presence of *gem*-dimethyl substitution greatly increased reaction rate of the palladium-catalyzed vinylcyclopropantion.

34 **35**

35% yield

The observation that palladium black was forming during the reaction led us to believe that the catalyst turnover problem lied in the rate of palladium re-oxidation. If the palladium(0) was not properly stabilized or not oxidized sufficiently fast, it was reasoned, the palladium(0) would aggregate into the inactive palladium black. Efforts to stabilize the palladium(0) in the reaction by adding pyridine ligands failed as the stability gained was at the cost of reactivity. The addition of copper acetate, however, either as stoichiometric oxidant or cooxidant led to the first examples of yield in excess of catalyst loading (Table 2). Yields were slightly in excess of catalyst loading at room temperature over extended reaction times in the presence of catalytic copper(II) acetate (entry 2). Increasing reaction temperature led to an increase in vinylcyclopropane yield (entry 3). Under optimized reaction conditions, a 50% yield of the vinylcyclopropane was isolated after twelve hours at 65 °C in the presence of 10 mol% palladium(II) acetate and 10 mol% copper(II) acetate (entry 4). A similar yield of vinylcyclopropane was isolated when stoichiometric amounts of copper acetate were used (entry 5).

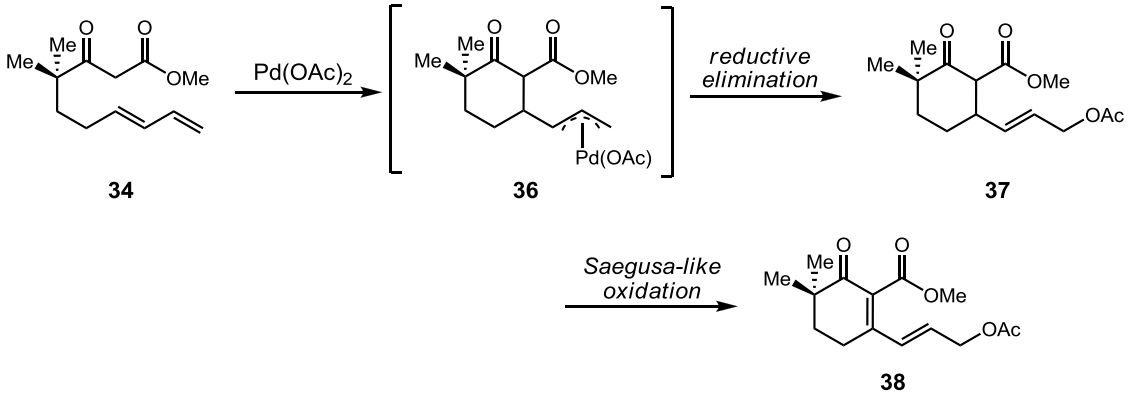
Table 2. Optimization of oxidizing conditions in the palladium-catalyzed vinylcyclopropanation.



entry	mol % $Pd(OAc)_2$	oxidant	temp. (°C)	time (h)	yield (%)
1	40	O_2	rt	18	35
2	20	$Cu(OAc)_2$ (0.2 eq), O_2	rt	48	25
3	20	$Cu(OAc)_2$ (0.2 eq), O_2	40	18	39
4	**10**	**$Cu(OAc)_2$ (0.1 eq), O_2**	**65**	**12**	**50**
5	**10**	**$Cu(OAc)_2$ (2.5 eq)**	**65**	**8**	**52**

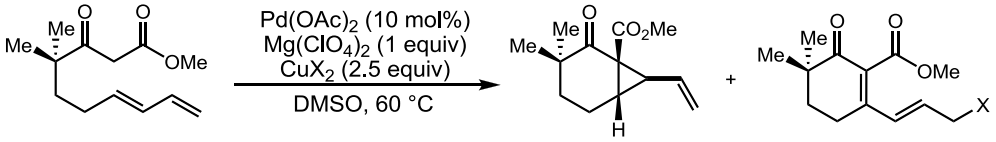
Under the newly optimized reaction conditions, it came to our attention that a significant portion of the substrate was being diverted to undesired allyl acetate side product **38** (Figure 14, A). This product, we postulated, was the result of a reductive elimination of palladium from π-allyl complex **36**, resulting in allyl acetate intermediate **37**. This side product was then oxidized under the reaction conditions to the doubly oxidized side product **38** observed (Figure 15).

Figure 15. Proposed mechanism for formation of sideproduct and B) optimized reaction conditions utilizing copper(II) isobutyrate for the palladium-catalyzed vinylcyclopropanation.



In order to slow the rate of this reductive elimination step, and thereby limit the production of the unwanted side product, changing the ligand environment of palladium was investigated. To do this, various copper (II) salts were employed, as ligands between the two metals are likely to exchange in solution (Table 3). The inclusion halide od toslyate containing copper (II) salts resulted in no reaction (entries 2-5), likely due to a relatively stable complex formed between the palladium and the counterions. Copper(II) acetylacetonate and copper(II) triflouroacetate halted formation of the sideproduct but also gave insufficient yields of desired product (entries 5 & 6). Copper(II) isobutyrate, on the other hand, gave improved yields of the vinylcyclopropane and completely suppressed the allylcarboxylate side product formation (entry 7).

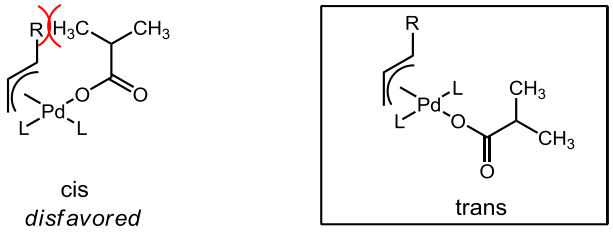
Table 3. Optimization of vinylcyclopropanation and suppression of dienyl sideproduct using various copper(II) salts.



entry	Cu(II) salt	VCP yield (%)	sideproduct yield (%)
1	$Cu(OAc)_2$	52	20
2	$CuCl_2$	–	--
3	$CuBr_2$	–	--
4	$Cu(OTf)_2$	–	--
5	$Cu(acac)_2$	9	--
6	$Cu(TFA)_2 \cdot H_2O$	21	--
7	**$Cu(O_2CiPr)_2$**	**74**	**--**

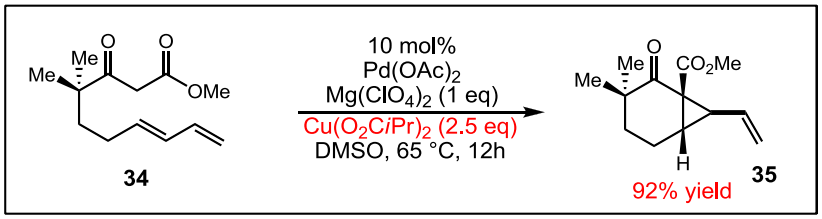
Suppression of allyl carboxylate side product formation is likely due to the bulkier nature of the isobutyrate counterion (Figure 16). In order for reductive elimination to occur, the allyl complex and isobutyrate counterion must adopt a *cis* relationship – bringing the two substituents in close enough proximity for bonding to occur. The bulky isobutyrate disfavors this *cis* structure by unfavorable steric interactions with the π-allyl group and therefore reductive elimination does not occur.

Figure 16. *Cis* versus *trans* relationships between the bulkier isobutyrate group and the allyl group of the substrate.



Having completely suppressed the allyl carboxylate side product formation, fully optimized conditions were quickly realized (Figure 17). A workup screen revealed that subsequent washings with saturated sodium bicarbonate and brine solutions results in superior yield of the vinylcyclopropane product. Washing with sodium bicarbonate solution serves to completely remove both the isobutyric acid and the remaining copper salts from the crude reaction mixture. These changes resulted in isolation of the vinylcyclopropane product in 92% yield.

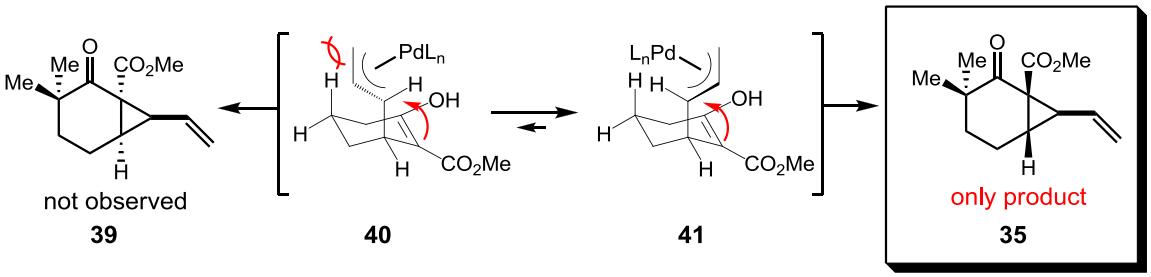
Figure 17. Fully optimized reaction conditions for the palladium-catalyzed vinylcyclopropanation.



Diastereoselectivity for the reaction was very good (10:1 by GC analysis) and the relative stereochemistry of the three formed stereogenic carbon centers were determined unambiguously by x-ray crystallographic analysis. The rationale for the diastereoselectivity is based on the direction in which the allyl group is situated in the palladium π-allyl intermediate complex (Figure 18). Assuming that nucleophilic attack occurs at the opposite face on the π-allyl as that of the palladium – in line with the observations of Bäckvall and coworkers – there are two possible orientations; one in which the allyl group is forced directly over the cyclohexane ring (intermediate **40**) and one in which it is directed away from the molecule (intermediate **41**). Unfavorable 1,3-

diaxial interactions between the bulkier allyl group and the axial protons of the substrate are minimized when the allyl group is pointed away from the cyclohexane ring, resulting in preference for vinylcyclopropane **35** in which the ester and vinyl groups are in a *cis* relationship.

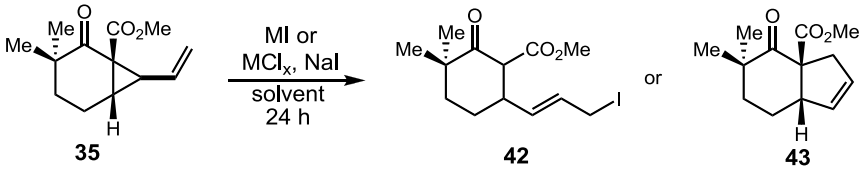
Figure 18. Diastereomeric rationale for the relative isomer product amounts.



With cyclopropanation conditions in hand, we next sought to transform our vinylcyclopropanes into the corresponding formal [4+1] cycloadducts. To our dismay, however, none of the standard conditions known to effect VCP-CP rearrangements were effective for the vinylcyclopropane substrates. The isomerization techniques attempted included known literature isomerization conditions like $(C_2H_4)Rh(acac)$,[13] LiI,[23] Et_2AlCl,[27] among others, all resulting in no conversion to the desired cyclopentene product. Subjecting the vinylcyclopropane to TMSI in CCl_4, however, led to clean conversion to allyl iodide **42** (Table 4, entry 1). It was then discovered that $MgCl_2$, $Mg(ClO_4)_2$, or $CeCl_3$ and NaI in CH_2Cl_2 led to the identical allyl iodide product (entries 2,3 & 4). While this was an important first step to our desired isomerization, the reaction needed to be rendered reversible in order to realize the completion of the formal [4+1] cycloaddition. A simple solvent screen revealed that the use of acetonitrile as solvent

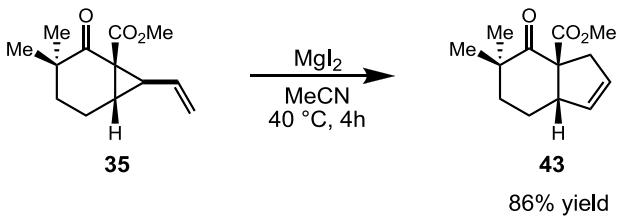
with $MgCl_2$ and NaI allowed the requisite equilibrium process and cyclopentene product **43** was observed exclusively (entry 5). A simpler protocol using MgI_2 in acetonitrile was also capable of effecting the VCP-CP rearrangement (entry 6). Later optimizations found that MgI_2 in acetonitrile at 40 °C over four hours gave optimal yields of the cyclopentene product (Figure 19).

Table 4. Optimization of VCP-CP rearrangement using metal iodides and metal chlorides with sodium iodide.



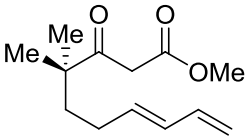
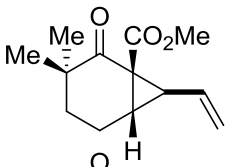
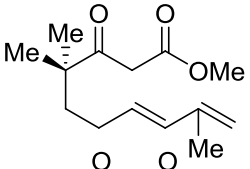
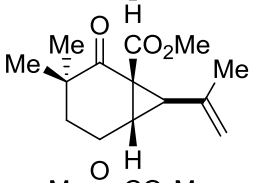
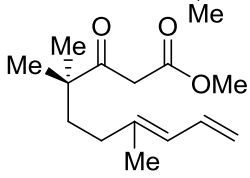
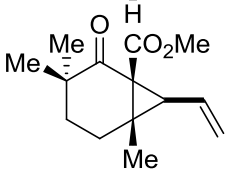
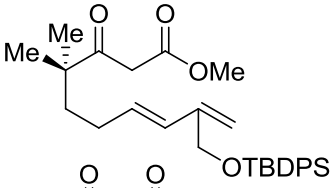
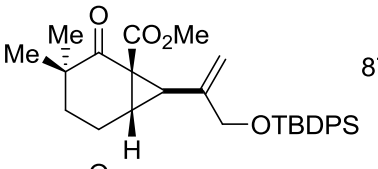
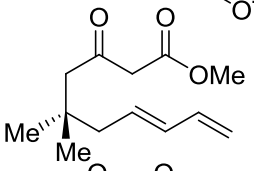
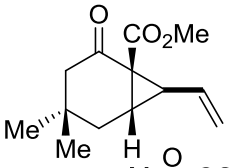
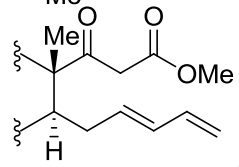
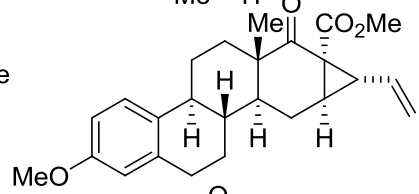
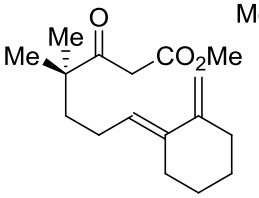
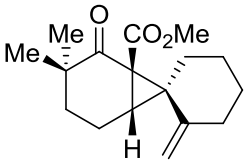
entry	MI or MCl_x, NaI	solvent	iodide conv. (%)	cyclopentene conv. (%)
1	TMSI	CCl_4	100	0
2	$MgCl_2$, NaI	CH_2Cl_2	100	0
3	$Mg(ClO_4)_2$, NaI	CH_2Cl_2	100	0
4	$CeCl_3 \bullet xH_2O$, NaI	CH_2Cl_2	100	0
5	$MgCl_2$, NaI	MeCN	0	100
6	**MgI_2**	**MeCN**	**0**	**100**

Figure 19. Final optimized conditions for isomerization of vinylcyclopropanes to cyclopentenes.



Having realized the first non-carbene carbogenic formal [4+1] cycloaddition, we turned our attention to examining the substrate scope of the annulation protocol (Table 5). In addition to the prototypical mono-substituted diene substrate, we found that substitution in the 2- or 4-positions is readily accommodated (entries 2 & 3). The presence of a silyl protecting group was also well tolerated by the reaction conditions (entry 4). Furthermore, cyclopropanation could be effected in reasonable yield with *gem*-dimethyl substitution in the δ-position to block undesired substrate oxidation (entry 5). Interestingly, efficient cyclization could be achieved even in a relatively complex setting, such as with the substrate derived from estrone (entry 6). Finally, we found our method was viable for the production of even highly strained cyclopropanes, albeit with a yield significantly lower than that of other substrates (entry 7). Overall, the diastereoselectivity was exceptional in all cases except in that of the estrone-derived substrate.

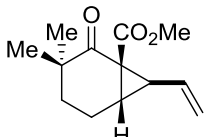
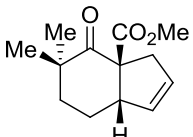
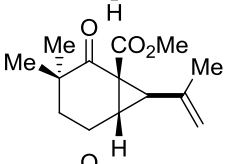
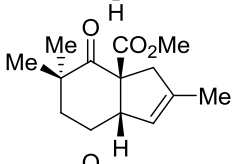
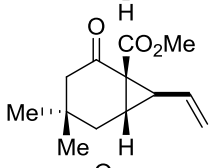
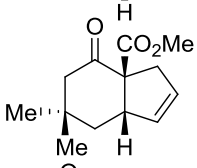
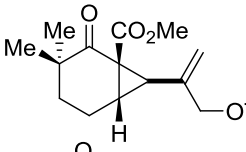
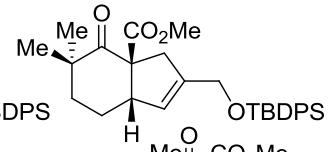
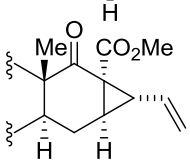
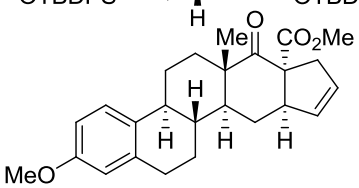
Table 5. Substrate scope of palladium-catalyzed vinylcyclopropanation reaction.[a]

Entry	Substrate	Product	% yield	d.r.[b]
1			92	10:1
2			93	>100:1
3			85	15:1
4			87	20:1
5			52	50:1
6[c]			59	3:1
7[d]			40 (BRSM)	13:1

[a] Reactions were run in the presence of $Pd(OAc)_2$ (10 mol%), $Mg(ClO_4)_2$ (1 equiv), $Cu(O_2C\textit{i}Pr)_2$ (2.5 equiv) in DMSO (0.1 M with respect to substrate) at 65 °C. [b] Diastereomeric ratios were determined by GC. [c] Diastereomeric ratios were determined by ^1H NMR analysis; minor diastereomer is epimeric at all cyclopropyl carbons. [d] 50% conversion.

We were also pleased to see that the VCP-CP rearrangement was also quite general and efficiently promoted the rearrangement of a number of our vinylcyclopropane products (Table 6). Methyl-substitution on the internal carbon of the vinyl group was tolerated, as well as that of the siloxymethylene substitution (entries 2 & 4). Substrates exhibiting *gem*-dimethyl substitution at the δ-position also underwent clean conversion (entry 3). The protocol was also effective at promoting rearrangement of the complex estrone-derived substrate (entry 5).

Table 6. Substrate scope of MgI_2-promoted VCP-CP rearrangement.[a]

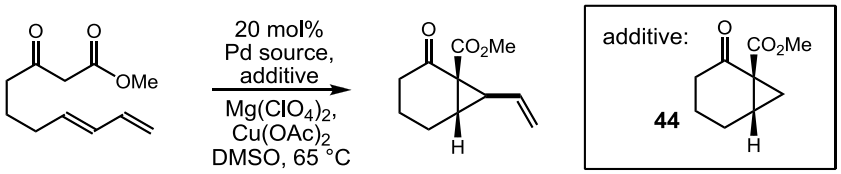
Entry	Substrate	Product	time (h)	% yield
1			4	86
2			6	75
3			6	80
4			8	74
5			8	78

[a] Reactions were run in the presence of MgI_2 (1.5 equiv) in CH_3CN at 40 °C.

We next sought to investigate conditions that would allow the newly discovered vinylcyclopropanation reaction to occur without the requisite *gem*-dimethyl substitution.

A number of ligand approaches, including a diverse set of monodentate and bidentate carboxylate ligands and bidentate sulfoxide ligands failed to render the reaction catalytic in substrates lacking the *gem*-dimethyl substitution. Due to fact that yields of the vinylcyclopropane approached that of the total catalyst load it was hypothesized that the non-*gem*-dimethyl substituted product formed during the reaction could actually render the palladium catalyst inactive. In order to investigate this hypothesis, compound **44** was added to the reaction mixture using both palladium(II) and palladium(0) catalysts (Table 7). In line with this hypothesis, the addition of the 'product-like' substrate prevented formation of vinylcyclopropane, *but only when starting with* Pd_2dba_3 (entry 4). This leads us to believe an inoperable complex is being formed between the product of the reaction and the palladium(0) intermediate that is formed in the reaction.

Table 7. Experiment showing product-like compound inhibits palladium-catalyzed vinylcyclopropanation.



entry	Pd source	additive (equiv.)	yield (%, ^{1}HNMR)
1	$Pd(OAc)_2$	--	~20
2	$Pd(OAc)_2$	1	~20
3	Pd_2dba_3	--	~20
4	**Pd_2dba_3**	**1**	**0**

Concluding Remarks

In conclusion, we have developed a formal [4+1] annulation protocol for the synthesis of [4.3.0] bicycles using a magnesium perchlorate-promoted palladium acetate-catalyzed vinylcyclopropanation followed by a magnesium iodide mediated VCP-CP rearrangement. The scope of the reaction protocol was investigated and a variety of functional groups and substitution patterns were tolerated. Our method offers an interesting and practical addition to known [4+1] annulation protocols as it is generally mild and avoids the necessity of generating carbene precursors to effect the transformation.

Efforts to render the reaction catalytic without the requisite *gem*-dimethyl substitution were unsuccessful and were due to an unreactive complex of the vinylcyclopropane product with the transient Pd(0) species.

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1) Portions of the research described in this chapter have been published as a communication: Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 2496.

2) For a review, see: Akhrem, A. A.; Titov, Y. A. *Total Steroid Synthesis*, Plenum Press: New York – London, **1970**.

3) For selected reviews see: (a) Fruhauf, H. *Chem. Rev.* **1997**, *97*, 523; (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

4) For a review, see: Wender, P. A.; Gamber, G. G.; and Williams, T. J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, **2005**; Chapter 13.

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Supporting Information

General Information:

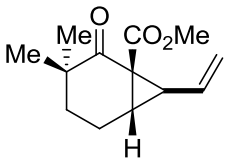
All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred by syringe under argon. Organic solutions were concentrated using a Buchi rotary evaporator. Diethyl ether, tetrahydrofuran, and methylene chloride (CH_2Cl_2) were dried using a J.C. Meyer solvent purification system. Triethylamine (Et_3N) and diisopropylamine were freshly distilled over CaH_2 under argon. All other commercial reagents were used as provided. Flash column chromatography was performed employing 32-63 μm silica gel (Dynamic Adsorbents Inc). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (EMD).

^1H and ^{13}C NMR were recorded in $CDCl_3$ on Bruker DRX-300, DRX-400, and DRX-500 spectrometers as noted. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet Avatar 370 DTGS (Thermo) using NaCl salt plates. High-resolution mass spectra (HRMS) were acquired at the Columbia University Mass Spectral Core Facility on a JEOL HX110 mass spectrometer using the technique (FAB+ or EI+) as noted. We are grateful to Dr. Yasuhiro Itagaki for acquiring the HRMS spectra. We are also grateful to Kevin Yurkerwich and Dr. Ged Parkin for X-ray data acquisition and solution.

Experimental Procedures:

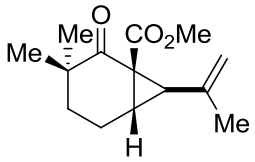
General procedure A: $Pd(OAc)_2$, $Mg(ClO_4)_2$, copper isobutyrate, and the dienyl-β-ketoester were dissolved in DMSO (0.1M with respect to dienyl-β-ketoester) in a 2 dram vial. The vial was then capped, warmed to 65 °C, and stirred until the dienyl-β-ketoester was completely consumed (2.5–18 h). The reaction mixture was then diluted with EtOAc to 20 times the volume of the reaction mixture and washed with equivalent volumes of saturated $NaHCO_3$ solution and brine. The organic phase was then dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford the title vinylcyclopropane.

General procedure B: The vinylcyclopropane was dissolved in acetonitrile (0.1 M) and MgI_2 was added. The reaction mixture was warmed to 40 °C until the vinylcyclopropane was consumed by TLC (4–8 h). The reaction mixture was then concentrated *in vacuo* and the crude residue was purified directly by flash chromatography to afford the title cyclopentene.



(±)-(1R,6S,7S)-Methyl 3,3-dimethyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure A from (*E*)-Methyl 5,5-dimethyl-3-oxoundeca-8,10-dienoate (20 mg, 0.089 mmol), $Pd(OAc)_2$ (2.0 mg, 8.9 μmol), $Mg(ClO_4)_2$ (20 mg, 0.089 mmol), and copper isobutyrate (53 mg, 0.22 mmol). Reaction

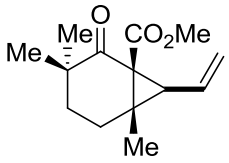
time: 18 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane as a colorless waxy solid (17.3 mg, 0.078 mmol, 87% yield, 10:1 d.r.[1] by GC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 8.7, 10.2, 17.1 Hz, 1H, C**H**=CH_2), 5.21 (d, *J* = 16.8 Hz, 1H, CH=C**H$_2$**), 5.09 (d, *J* = 10.2 Hz, 1H, CH=C**H$_2$**), 3.68 (s, 3H, CO_2C**H$_3$**), 2.20–2.08 (m, 3H, C**H$_2$**CH_2 + C**H**$CH=CH_2$), 1.95–1.87 (m, 1H, C**H$_2$**CH_2), 1.58–1.44 (m, 2H, C**H$_2$**CH_2 + C**H**), 1.10 (s, 3H, $C(C$**H$_3$**$)_2$), 1.07 (s, 1H, $C(C$**H$_3$**$)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 169.0, 133.6, 117.9, 52.5, 42.8, 40.1, 32.2, 31.7, 29.7, 24.9, 24.0, 17.4; IR (thin film) 2951, 2867, 1713, 1436, 1329, 1262, 1237, 1201, 1122, 980 911 cm^{-1}; HRMS (EI+) *m/z* = 222.1250 calcd for $C_{13}H_{18}O_3$ $[M]^+$, found 222.1259.



(±)-(1R,6S,7R)-Methyl 3,3-dimethyl-2-oxo-7-(prop-1-en-2-yl)bicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure A from (E)-methyl 4,4,9-trimethyl-3-oxodeca-7,9-dienoate (20 mg, 0.084 mmol), $Pd(OAc)_2$ (1.9 mg, 8.4 μmol), $Mg(ClO_4)_2$ (19 mg, 0.084 mmol), and copper isobutyrate (50 mg, 0.21 mmol). Reaction time: 18 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane as a colorless oil (18.5 mg, 0.078 mmol, 93% yield, >100:1 d.r. by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1H,

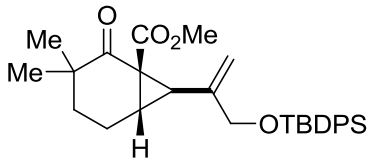
[1] Relative stereochemistry of major diastereomer was determined by X-ray analysis (see page 63). The stereochemistry of all other compounds was determined by analogy unless otherwise noted.

C=C**H**$_2$), 4.80 (s, 1H, C=C**H**$_2$), 3.67 (s, 3H, CO_2C**H**$_3$), 2.43–2.36 (m, 1H, C**H**$_2$$CH_2$), 2.23–2.09 (m, 2H, C**H**$_2$$CH_2$ + C**H**C(CH_3)=CH_2), 1.97–1.87 (m, 1H, C**H**$_2$$CH_2$), 1.80 (s, 3H, C**H**$_3$C=$CH_2$), 1.63–1.45 (m, 2H, C**H**$_2$$CH_2$ + C**H**), 1.12 (s, 3H, C(C**H**$_3$)$_2$), 1.11 (s, 3H, C(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 168.1, 139.6, 113.2, 52.4, 42.7, 41.2, 33.7, 31.9, 26.2, 25.4, 24.8, 22.8, 17.5; IR (thin film) 2949, 2869, 1728, 1693, 1436, 1343, 1274, 1231, 1195, 1163, 1058, 980, 893 cm^{-1}; HRMS (EI+) *m/z* = 237.1485 calcd for $C_{14}H_{21}O_3$ $[MH]^+$, found 237.1487.

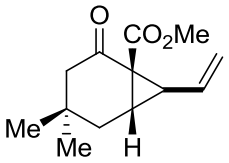


(±)-(1S,6S,7S)-Methyl 3,3,6-trimethyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure A from (E)-methyl 4,4,7-trimethyl-3-oxodeca-7,9-dienoate (20 mg, 0.084 mmol), $Pd(OAc)_2$ (1.9 mg, 8.4 μmol), $Mg(ClO_4)_2$ (19 mg, 0.084 mmol), and copper isobutyrate (50 mg, 0.21 mmol). Reaction time: 6 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane as a colorless oil (16.7 mg, 0.071 mmol, 84% yield, 15:1 d.r. by GC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, 9.5, 10.3, 17.0 Hz, 1H, C**H**=CH_2), 5.22 (dd, *J* = 1.7, 17.0 Hz, 1H, CH=C**H**$_2$), 5.15 (dd, *J* = 1.7, 10.3 Hz, 1H, CH=C**H**$_2$), 3.68 (s, 3H, CO_2C**H**$_3$), 2.16 (d, *J* = 9.5 Hz, 1H, C**H**CH=CH_2), 2.02–1.83 (m, 2H, C**H**$_2$$CH_2$), 1.66–1.43 (m, 2H, CH_2C**H**$_2$), 1.20 (s, 3H, C**C**H$_3$), 1.10 (s, 3H, C(C**H**$_3$)$_2$), 1.09 (s, 3H, C(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 168.2, 131.9, 118.1, 52.2, 46.8, 41.5, 33.0, 31.4, 26.2, 25.3, 25.0, 17.6; IR (thin film) 2953, 2930, 2872,

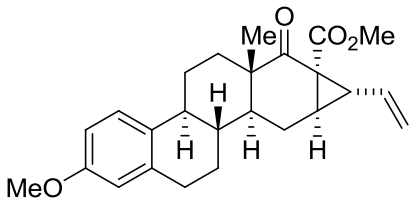
1740, 1695, 1458, 1435, 1318, 1223, 1206, 1122, 1084, 981, 909, 702 cm^{-1}; HRMS (FAB+) *m/z* = 237.1485 calcd for $C_{14}H_{21}O_3$ $[MH]^+$, found 237.1474.



(±)-(1R,6S,7R)-Methyl 7-(3-(tert-butyldiphenylsilyloxy)prop-1-en-2-yl)-3,3-dimethyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure A from (E)-methyl 9-((tert-butyldiphenylsilyloxy)methyl)-4,4-dimethyl-3-oxodeca-7,9-dienoate (19 mg, 0.039 mmol), $Pd(OAc)_2$ (0.9 mg, 3.9 μmol), $Mg(ClO_4)_2$ (8.6 mg, 0.039 mmol), and copper isobutyrate (23 mg, 0.097 mmol). Reaction time: 18 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane as a colorless oil (14 mg, 0.029 mmol, 75% yield, 20:1 d.r. by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.63 (m, 4H, Ar**H**), 7.48–7.33 (m, 6H, Ar**H**), 5.31 (s, 1H, C=C**H$_2$**), 4.92 (s, 1H, C=C**H$_2$**), 4.18 (s, 2H, CC**H$_2$**OSi), 3.58 (s, 3H, CO_2CH_3), 2.47–2.40 (s, 1H, C**H$_2$**CH_2), 2.27 (d, *J* = 7.1 Hz, 1H, C**H**C(C)=CH_2)), 2.23–2.08 (m, 1H, C**H$_2$**CH_2), 1.98–1.87 (m, 1H, C**H$_2$**CH_2), 1.57–1.46 (m, 2H, C**H$_2$**CH_2 + C**H**), 1.07 (s, 3H, C(C**H$_3$**)$_2$), 1.05 (s, 3H, C(C**H$_3$**)$_2$), 1.02 (s, 9H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 168.0, 142.4, 135.7, 133.6, 129.8, 127.9, 111.7, 66.4, 52.5, 42.7, 42.1, 31.9, 28.9, 26.9, 25.6, 25.3, 25.2, 19.4, 17.5; IR (thin film) 2932, 2857, 1727, 1428, 1261, 1112, 818, 702 cm^{-1}; HRMS (FAB+) *m/z* = 491.2612 calcd for $C_{30}H_{39}O_4Si$ $[MH]^+$, found 491.2629.

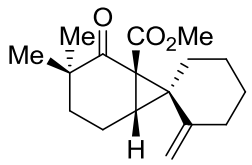


(±)-(1R,6S,7S)-Methyl 4,4-dimethyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure A from (*E*)-Methyl 6,6-dimethyl-3-oxoundeca-8,10-dienoate (20 mg, 0.089 mmol), $Pd(OAc)_2$ (2.0 mg, 8.9 μmol), $Mg(ClO_4)_2$ (20 mg, 0.089 mmol), and copper isobutyrate (53 mg, 0.22 mmol). Reaction time: 8 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane as a colorless oil (10.3 mg, 0.046 mmol, 52% yield, 50:1 d.r. by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (ddd, 8.1, 10.2, 16.9 Hz, 1H, C**H**=CH_2), 5.24 (dd, 1.3, 16.9 Hz, 1H, CH=C**H$_2$**), 5.12 (dd, 1.3, 10.2 Hz, 1H, CH=C**H$_2$**), 3.76 (s, 3H, CO_2C**H$_3$**), 2.28–2.09 (m, 3H, C(=O)C**H$_2$** + C**H**C=CH_2), 2.05–1.95 (m, 2H, C**H$_2$**), 1.62–1.53 (m, 1H, C**H**), 0.99 (s, 6H, C(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 168.1, 134.1, 117.9, 52.7, 50.1, 44.5, 42.0, 36.7, 30.8, 29.5, 26.3, 19.1; IR (thin film) 2956, 2871, 1731, 1694, 1436, 1345, 1275, 1252, 1208, 1168, 1055, 982 cm^{-1}; HRMS (FAB+) *m/z* = 223.1329 calcd for $C_{13}H_{19}O_3$ $[MH]^+$, found 223.1337.

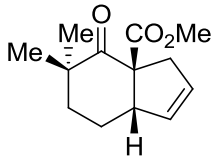


Estrone-derived vinylcyclopropane: Prepared according to general procedure A from estrone-derived dienyl-β-ketoester (20 mg, 0.050 mmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol), $Mg(ClO_4)_2$ (11 mg, 0.050 mmol), and copper isobutyrate (30 mg, 0.13 mmol). Reaction time: 18 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane (11.7 mg, 0.023 mmol, 59% yield, 3:1 d.r. by ^{1}H NMR[2]) as a colorless waxy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, Ar**H**), 6.72 (dd, *J* = 2.5, 8.6 Hz, 1H, Ar**H**), 6.63 (d, *J* = 2.5 Hz, 1H, Ar**H**), 5.91 (ddd, *J* = 8.9, 10.4, 17.2 Hz, 0.75 × 1H, C**H**=CH_2, major), 5.68 (ddd, *J* = 8.4, 10.2, 17.0 Hz, 0.25 × 1H, C**H**=CH_2, minor), 5.27 (dd, *J* = 1.4, 17.2 Hz, 1H, CH=C$\mathbf{H_2}$), 5.13 (dd, *J* = 1.4, 10.2 Hz, 1H, CH=C$\mathbf{H_2}$), 3.78 (s, 3H, ArOC$\mathbf{H_3}$), 3.73 (t, *J* = 4.1 Hz, 3H, $CO_2C\mathbf{H_3}$), 2.91–2.81 (m, 2H, ArC$\mathbf{H_2}$), 2.44–2.10 (m, 4H), 2.10–1.94 (m, 2H), 1.83–1.59 (m, 2H), 1.49–1.13 (m, 5H), 1.09 (s, 0.75 × 3H, C$\mathbf{H_3}$), 1.04 (s, 0.25 × 3H, C$\mathbf{H_3}$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.8, 169.2, 157.8, 137.6, 134.3, 133.7, 126.6, 121.2, 113.6, 111.9, 55.3, 52.6, 46.7, 42.6, 39.9, 39.6, 38.6, 33.5, 32.2, 30.1, 28.5, 26.1, 26.0, 21.6, 15.3; IR (thin film) 2936, 2864, 1721, 1610, 1501, 1435, 1252, 1199, 1147, 1039, 734 cm^{-1}; HRMS (FAB+) *m/z* = 394.2139 calcd for $C_{25}H_{30}O_4$ $[M]^+$, found 394.2139.

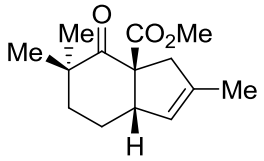
[2] Configuration of major diastereomer was determined by NOESY and COSY (see attached spectra) at 400 MHz. Configuration of minor diastereomer was not determined.



(±)-(1R,1'R,6S)-Methyl 3,3-dimethyl-2'-methylene-2-oxospiro[bicyclo[4.1.0]heptane-7,1'-cyclohexane]-1-carboxylate: Prepared according to general procedure A from (E)-Methyl 4,4-dimethyl-7-(2-methylenecyclohexylidene)-3-oxoheptanoate (20 mg, 0.072 mmol), $Pd(OAc)_2$ (1.6 mg, 7.2 μmol), $Mg(ClO_4)_2$ (16 mg, 0.072 mmol), and copper isobutyrate (42 mg, 0.18 mmol). Reaction time: 2.5 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title vinylcyclopropane as a colorless oil (4.0 mg, 0.014 mmol, 40% yield based on recovered starting material, 28:1 d.r. by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (s, 1H, C=C**H$_2$**), 4.74 (s, 1H, C=C**H$_2$**), 3.64 (s, 3H, CO_2C**H$_3$**), 2.50–2.43 (m, 1H, C**H$_2$**C=CH_2), 2.34–2.25 (m, 1H, C**H$_2$**C=CH_2), 2.25–2.12 (m, 1H, C**H$_2$**CH_2), 2.05–1.92 (m, 1H, C**H$_2$**CH_2), 1.92–1.79 (m, 1H, C**H$_2$**CH_2), 1.79–1.55 (m, 6H, C**H$_2$**C**H$_2$**C**H$_2$**), 1.40–1.24 (m, 2H, C**H$_2$**CH_2), 1.19 (s, 3H, C(C**H$_3$**)$_2$), 1.06 (s, 3H, C(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 168.5, 148.1, 110.1, 52.5, 44.3, 43.8, 40.9, 37.1, 35.3, 31.5, 29.2, 28.4, 24.6, 24.0, 23.4, 15.3; IR (thin film) 2935, 2864, 1727, 1708, 1434, 1239, 1201, 1074, 990, 891 cm^{-1}; HRMS (FAB+) *m/z* = 277.1798 calcd for $C_{17}H_{25}O_3$ $[MH]^+$, found 277.1788.

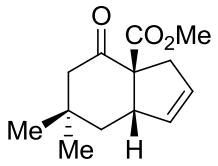


(±)-(3aS,7aS)-Methyl 6,6-dimethyl-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-indene-7a-carboxylate: Prepared according to general procedure B from (±)-(1R,6S,7S)-methyl 3,3-dimethyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate (10 mg, 0.045 mmol) and MgI_2 (19 mg, 0.068 mmol). Reaction time: 4 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title cyclopentene (8.6 mg, 39 μmol, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67–5.61 (m, 1H, C**H**=C**H**), 5.53–5.48 (m, 1H, C**H**=C**H**), 3.68 (s, 3H, $CO_2C\mathbf{H_3}$), 3.67–3.60 (m, 1H, C**H**), 3.09 (dq, *J* = 2.2, 17.0 Hz, 1H, CH=CHC$\mathbf{H_2}$), 2.83 (dq, *J* = 2.2, 16.9 Hz, 1H, CH=CHC$\mathbf{H_2}$), 2.17–2.04 (m, 1H, C$\mathbf{H_2}CH_2$), 1.69–1.60 (m, 2H, C$\mathbf{H_2}CH_2$), 1.60–1.48 (m, 1H, C$\mathbf{H_2}CH_2$), 1.12 (s, 3H, C(C$\mathbf{H_3}$)$_2$), 1.08 (s, 3H, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 172.9, 133.3, 129.0, 64.0, 52.7, 50.6, 44.8, 41.5, 35.5, 27.1, 26.1, 23.4; IR (thin film) 2954, 2872, 1736, 1716, 1436, 1242, cm^{-1}; HRMS (EI+) *m/z* = 222.1250 calcd for $C_{13}H_{18}O_3$ $[M]^+$, found 222.1245.



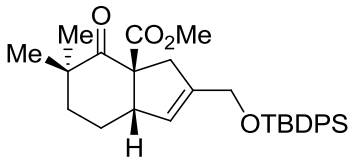
(±)-(3aS,7aS)-Methyl 2,6,6-trimethyl-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-indene-7a-carboxylate: Prepared according to general procedure B from (±)-(1R,6S,7R)-Methyl 3,3-dimethyl-2-oxo-7-(prop-1-en-2-yl)bicyclo[4.1.0]heptane-1-carboxylate (10 mg, 0.042

mmol) and MgI_2 (19 mg, 0.063 mmol). Reaction time: 6 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title cyclopentene (7.5 mg, 32 μmol, 75% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12–5.06 (m, 1H, C=C**H**), 3.68 (s, 3H, $CO_2C\mathbf{H_3}$), 3.64–3.56 (m, 1H, C**H**), 2.97 (d, J = 16.6 Hz, 1H, $CH=C(CH_3)C\mathbf{H_2}$), 2.74 (d, J = 16.6 Hz, 1H, $CH=C(CH_3)C\mathbf{H_2}$), 2.12–2.98 (m, 1H, $C\mathbf{H_2}CH_2$), 1.71–1.61 (m, 5H, $C\mathbf{H_2}CH_2$ + $CH=CC\mathbf{H_3}$), 1.56–1.44 (m, 1H, $C\mathbf{H_2}CH_2$), 1.11 (s, 3H, $C(C\mathbf{H_3})_2$), 1.09 (s, 3H, $C(C\mathbf{H_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 173.0, 138.8, 126.9, 64.6, 52.6, 50.7, 45.3, 44.9, 35.6, 27.1, 26.2, 23.8, 16.4; IR (thin film) 2933, 2867, 1737, 1709, 1455, 1435, 1240, 1060, 1020 cm^{-1}; HRMS (FAB+) *m/z* = 237.1485 calcd for $C_{14}H_{21}O_3$ $[MH]^+$, found 237.1481.

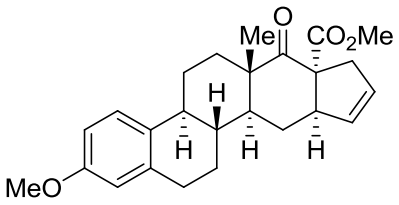


(±)-(3aS,7aS)-Methyl 5,5-dimethyl-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-indene-7a-carboxylate: Prepared according to general procedure B from (±)-(1R,6S,7S)-Methyl 4,4-dimethyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate (5.2 mg, 0.023 mmol) and MgI_2 (10 mg, 0.035 mmol). Reaction time: 6 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title cyclopentene (4.1 mg, 18 μmol, 80% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72–5.62 (m, 2H, C**H**=C**H**), 3.72 (s, 3H, $CO_2C\mathbf{H_3}$), 3.67–3.58 (m, 1H, C**H**), 2.96 (dq, *J* = 16.7, 1.7 Hz, 1H, $C(O)C\mathbf{H_2}$), 2.87 (dq, *J* = 16.7, 1.9 Hz, $C(O)C\mathbf{H_2}$), 2.33 (dd, *J* = 1.3, 14.3 Hz, 1H, $C\mathbf{H_2}CH=CH$), 2.23 (d, *J* = 14.3 Hz, 1H, $C\mathbf{H_2}CH=CH$), 1.90 (ddd, *J* = 1.0, 6.2, 13.9 Hz,

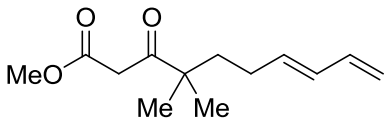
1H, C**H**$_2$), 1.40 (dd, *J* = 8.4, 13.9 Hz, 1H, C**H**$_2$), 1.06 (s, 3H, C(C**H**$_3$)$_2$), 0.97 (s, 1H, C(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 172.8, 134.6, 127.7, 64.8, 52.7, 52.1, 49.6, 41.1, 38.0, 35.1, 29.6, 27.9; IR (thin film) 2957, 1720, 1435, 1247, 1163, 1063 cm^{-1}; HRMS (FAB+) *m/z* = 223.1329 calcd for $C_{13}H_{19}O_3$ $[MH]^+$, found 223.1324.



(±)-(3aS,7aS)-Methyl 2-((tert-butyldiphenylsilyloxy)methyl)-6,6-dimethyl-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-indene-7a-carboxylate: Prepared according to general procedure B from (±)-(1R,6S,7R)-Methyl 7-(3-(tert-butyldiphenylsilyloxy)prop-1-en-2-yl)-3,3-dimethyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (5.0 mg, 0.010 mmol) and MgI_2 (4.3 mg, 0.015 mmol). Reaction time: 8 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title cyclopentene (3.7 mg, 7.4 μmol, 74% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4H, Ar**H**), 7.45–7.33 (m, 6H, Ar**H**), 5.44–5.38 (m, 1H, C=C**H**), 4.17 (s, 2H, C**H**$_2$OSi), 3.71–3.63 (m, 4H, C**H**), 3.02 (d, *J* = 16.3, 1H, CH=CC**H**$_2$), 2.76 (d, *J* = 16.3 Hz, 1H, CH=CC**H**$_2$), 2.19–2.03 (m, 1H, C**H**$_2$CH$_2$), 1.73–1.49 (m, 3H, C**H**$_2$C**H**$_2$), 1.12 (s, 3H, C(C**H**$_3$)$_2$), 1.10 (s, 3H, C(C**H**$_3$)$_2$), 1.05 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 172.8, 142.5, 135.6, 133.7, 129.8, 127.8, 126.6, 64.3, 62.7, 52.7, 50.2, 44.9, 41.3, 35.6, 27.1, 26.9, 26.1, 23.5, 19.4; IR (thin film) 2930, 2856, 1736, 1709, 1459, 1428, 1245, 1112, 1059, 823, 742, 702 cm^{-1}; HRMS (FAB+) *m/z* = 491.2612 calcd for $C_{30}H_{39}O_4$ $[M]^+$, found 491.2639.



Estrone-derived cyclopentene: Prepared according to general procedure B from the estrone-derived vinylcyclopropane (11.7 mg, 0.030 mmol) and MgI_2 (12 mg, 0.045 mmol). Reaction time: 8 h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to afford the title cyclopentene (9.2 mg, 23 μmol, 78% yield) as a colorless waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 1H, Ar**H**), 6.72 (dd, J = 2.7, 8.6 Hz, 1H, Ar**H**), 6.63 (d, J = 3.0 Hz, 1H, Ar**H**), 5.69–5.63 (m, 1H, C**H**=CH), 5.47–5.42 (m, 1H, CH=C**H**), 3.92–3.86 (m, 1H, C**H**), 3.78 (s, 3H, ArOC**H$_3$**), 3.69 (s, 3H, CO_2C**H$_3$**), 3.49–3.41 (m, 1H, CH=CHC**H$_2$**), 2.91–2.83 (m, 2H, ArC**H$_2$**), 2.59–2.51 (m, 1H, CH=CHC**H$_2$**), 2.41–2.07 (m, 4H), 1.99 (dt, J = 3.7, 13.9 Hz, 1H), 1.93–1.81 (m, 1H), 1.71–1.61 (m, 1H), 1.51–1.34 (m, 3H), 1.34–1.21 (m, 1H), 1.02 (s, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 172.5, 158.0, 138.1, 134.8, 132.8, 129.8, 126.6, 113.8, 112.0, 63.3, 55.6, 52.9, 49.0, 48.4, 44.5, 42.9, 42.6, 39.2, 33.9, 30.4, 26.9, 26.1, 24.6; IR (thin film) 2949, 2867, 1734, 1707, 1610, 1502, 1451, 1434, 1231, 1147, 1052, 1033, 968, 728 cm^{-1}; HRMS (FAB+) *m/z* = 394.2139 calcd for $C_{25}H_{30}O_4$ $[M]^+$, found 394.2133.

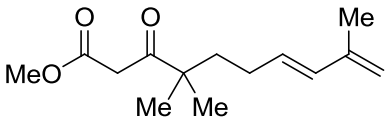


75:25, keto/enol

(*E*)-Methyl 4,4-dimethyl-3-oxodeca-7,9-dienoate: To a suspension of NaH (60% in oil, 1.75 g, 43.7 mmol) in THF (180 mL) at 0 °C was added methyl 4-methyl-3-oxovalerate (6.302 g, 43.74 mmol) in THF (30 mL) dropwise. The reaction was stirred for 15 min at 0 °C then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 17.5 mL, 43.7 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C and (*E*)-6-iodohexa-1,3-diene[3] (10.9 g, 52.5 mmol) was added. The reaction was then allowed to stir overnight at 4 °C (cold room). The reaction was quenched by addition of saturated NH_4Cl solution (150 mL) followed by extraction with ether 200 mL × 3). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound (2.73 g, 12.2 mmol, 28% yield) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.27 (s, 0.25 × 1H, CH=CO**H**, enol), 6.29 (dt, *J* = 10.3, 17.1 Hz, 1H, CH=CHC**H**=CH_2), 6.11–5.96 (m, 1H, CH=C**H**CH=CH_2), 5.72–5.59 (m, 1H, CH_3C**H**=CH), 5.10 (d, *J* = 16.9 Hz, 1H, CH=C$\mathbf{H_2}$), 5.04 (s, 0.25 × 1H, C**H**=COH, enol), 4.98 (d, *J* = 10.1 Hz, 1H, CH=C$\mathbf{H_2}$), 3.73 (s, 3H, $CO_2C\mathbf{H_3}$), 3.53 (s, 0.75 × 2H, C(O)C$\mathbf{H_2}$C(O), keto), 2.05–1.93 (m, 2H, C=CHC$\mathbf{H_2}$), 1.66–1.56 (m, 2H $CH_2C\mathbf{H_2}$), 1.16 (s, 0.75 × 6H, C(C$\mathbf{H_3}$)$_2$, keto), 1.13 (s, 0.25 × 6H, C(C$\mathbf{H_3}$)$_2$, enol); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 184.5 (enol), 173.5 (enol), 168.1, 137.2 (enol), 137.0, 134.9 (enol), 134.1, 131.4, 131.1 (enol), 115.3, 114.9 (enol), 86.9 (enol), 52.2, 51.1 (enol), 48.1, 44.0,

[3] Brodney, M.; O'Leary, J.; Hansen, J.; Giguere, R. *Synth. Commun.* **1995**, *25*, 521.

39.7 (enol), 39.0, 27.8 (enol) 27.7, 25.5, 24.0; IR (thin film) 3439, 2958, 1738, 1440, 1270, 665 cm^{-1}; HRMS (FAB+) *m/z* = 225.1485 calcd for $C_{13}H_{21}O_3$ $[MH]^+$, found 225.1476.



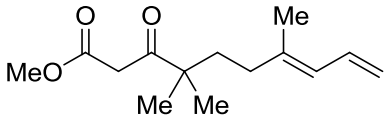
80:20, keto/enol

(*E*)-Methyl 4,4,9-trimethyl-3-oxodeca-7,9-dienoate: To CH_2Cl_2 (75 mL) was added triphenylphosphine (6.14 g, 23.0 mmol), imidazole (1.56 g, 23.0 mmol), and iodine (5.84 g, 23.0 mmol). (*E*)-5-Methylhexa-3,5-dien-1-ol[4] (1.90 g, 16.9 mmol) was added. Reaction was stirred for 15 min then diluted with pentane (50 mL) then filtered through 2" of silica, eluting with pentane. The collected solution was then concentrated *in vacuo* to yield the corresponding iodide that was used immediately in the following procedure.

To a suspension of NaH (60% in oil, 0.405 g, 10.1 mmol) in THF (45 mL) at 0 °C was added methyl 4-methyl-3-oxovalerate (1.46 g, 43.7 mmol) in THF (5 mL) dropwise. The reaction was stirred for 15 min at 0 °C then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 4.1 mL, 10.1 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C and the above iodide (2.70 g, 12.2 mmol) was added. The reaction was then allowed to stir overnight at 4 °C (cold room). The reaction was quenched by addition of saturated NH_4Cl solution (50 mL) followed by extraction with ether (75 mL × 3). The combined organic layers were washed with brine (75 mL), dried ($MgSO_4$) and

[4] Joyce, R.; Gainor, J.; Weinreb, S. *J. Org. Chem.* **1987**, *52*, 1177.

concentrated *in vacuo*. The crude product was purified by flash chromatography (9:1, hexanes/EtOAc) to yield the title compound (0.590 g, 2.48 mmol, 24% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.25 (s, 0.20 × 1H, CH=CO**H**, enol), 6.08 (d, J = 15.2 Hz, 1H, CH=C**H**C(CH_3)=CH_2), 5.62–5.48 (m, 1H, CH_2C**H**=CH), 4.99 (s, 0.20 × 1H, C**H**=COH, enol), 4.81 (s, 0.80 × 2H, C=C**H$_2$**, keto), 4.79 (s, 0.20 × 1H, C=C**H$_2$**, enol), 3.67 (s, 3H, CO_2C**H$_3$**), 3.48 (s, 0.80 × 2H, C(O)C**H$_2$**C(O), keto), 2.02–1.91 (m, 2H, C=CHC**H$_2$**CH_2), 1.76 (s, 3H, C(C**H$_3$**)=CH_2), 1.63–1.54 (m, 2H, C**H$_2$**CH_2), 1.11 (s, 0.80 × 6H, C(C**H$_3$**)$_2$, keto), 1.08 (s, 0.20 × 6H, C(C**H$_3$**)$_2$, enol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 184.5 (enol), 173.4 (enol), 168.0, 142.0 (enol), 141.8, 133.3, 132.8 (enol), 130.3 (enol), 129.6, 114.7, 114.3 (enol), 86.8 (enol), 52.1, 51.0 (enol), 48.0, 44.0, 39.9 (enol), 39.2, 27.9, 25.4, 23.9, 18.6; IR (thin film) 2970, 2952, 1751, 1708, 1619, 1437, 1318, 1270, 1217, 1154, 1027, 967, 884 cm^{-1}; HRMS (FAB+) *m/z* = 239.1642 calcd for $C_{14}H_{23}O_3$ $[MH]^+$, found 239.1633.

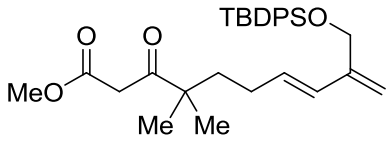


85:15, keto/enol

(*E*)-Methyl 4,4,7-trimethyl-3-oxodeca-7,9-dienoate: To a suspension of NaH (60% in oil, 0.516 g, 12.9 mmol) in THF (50 mL) at 0 °C was added methyl 4-methyl-3-oxovalerate (1.86 g, 12.9 mmol) in THF (5 mL) dropwise. The reaction was stirred for 15 min at 0 °C then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 5.2 mL, 12.9 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C and (*E*)-

6-iodo-4-methylhexa-1,3-diene[5] (3.45 g, 15.5 mmol) was added. The reaction mixture was then allowed to stir overnight at 4 °C (cold room). The reaction mixture was quenched by addition of saturated NH_4Cl solution (50 mL) followed by extraction with ether (75 mL × 3). The combined organic layers were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash chromatography (9:1, hexanes/EtOAc) to yield the title compound (0.788 g, 3.31 mmol, 21% yield) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.25 (s, 0.15 × 1H, CH=CO**H**, enol), 6.47 (dt, *J* = 10.8, 17.4 Hz, 1H, C=CHC**H**=CH_2), 5.78 (d, *J* = 10.8 Hz, 1H, C=C**H**CH=CH_2), 5.02 (d, J = 16.7 Hz, 1H, CH=C$\mathbf{H_2}$), 4.98 (s, 0.15 × 1H, C**H**=COH, enol), 4.92 (d, *J* = 10.2 Hz, 1H, CH=C$\mathbf{H_2}$), 3.65 (s, 3H, $CO_2C\mathbf{H_3}$), 3.47 (s, 0.85 × 2, C(O)C$\mathbf{H_2}$C(O), keto), 2.03–1.93 (m, 0.15 × 2H, C=C(CH_3)C$\mathbf{H_2}$, enol), 1.92–1.81 (m, 0.85 × 2H, C=C(CH_3)C$\mathbf{H_2}$, keto), 1.69 (s, 3H, C=C(C$\mathbf{H_3}$)), 1.64–1.54 (m, 2H, CC$\mathbf{H_2}CH_2$), 1.10 (s, 0.85 × 6H, C(C$\mathbf{H_3}$)$_2$, keto), 1.07 (s, 0.15 × 6H, C(C$\mathbf{H_3}$)$_2$, enol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 184.5 (enol), 173.4 (enol), 168.0, 139.3 (enol), 138.6, 133.1, 132.6 (enol), 125.6, 125.3 (enol), 115.0, 114.6 (enol), 86.8 (enol), 52.1, 51.0 (enol), 47.9, 43.9, 38.5 (enol), 38.0, 34.8 (enol), 34.6, 27.4 (enol), 25.4, 23.9, 16.6; IR (thin film) 3485, 2970, 2873, 1748, 1705, 1620, 1438, 1286, 1219, 1157, 1022, 736 cm^{-1}; HRMS (FAB+) *m/z* = 239.1642 calcd for $C_{14}H_{23}O_3$ $[MH]^+$, found 239.1640.

[5] Li, C.; Wang, C.; Liang, B.; Zhang, X.; Deng, L.; Liang, S.; Chen, J.; Wu, Y.; Yang, Z. *J. Org. Chem.* **2006**, *71* , 6892.

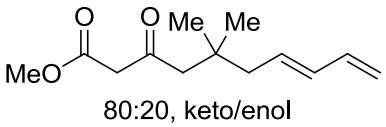


78:22, keto/enol

(*E*)-Methyl 9-((tert-butyldiphenylsilyloxy)methyl)-4,4-dimethyl-3-oxodeca-7,9-dienoate: To a suspension of NaH (60% in oil, 22.0 mg, 0.56 mmol) in THF (2 mL) at 0 °C was added methyl 4-methyl-3-oxovalerate (81 mg, 0.56 mmol) in THF (300 μL) dropwise. The reaction was stirred for 15 min at 0 °C then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 225 μL, 0.56 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 10 min then allowed to warm to 0 °C and (*E*)-(6-bromo-2-methylenehex-3-enyloxy)(tert-butyl)diphenylsilane[6] (0.770 g, 1.79 mmol) was added. The reaction mixture was then allowed to stir overnight at 4 °C (cold room). The reaction mixture was quenched by addition of saturated NH_4Cl solution (5 mL) followed by extraction with ether (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash chromatography (9:1, hexanes/EtOAc) to yield the title compound (19 mg, 39 μmol, 7% yield) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.26 (s, 0.22 × 1H, CH=CO**H**, enol), 7.75–7.64 (m, 4H, Ar**H**), 7.48–7.30 (m, 6H, Ar**H**), 6.07 (d, *J* = 16.0 Hz, 1H, CH=C**H**C(CH_2OTBDPS)=CH_2), 5.57–5.41 (m, 1H, CH_2C**H**=CH), 5.39 (s, 1H, C=C**H$_2$**), 5.06 (s, 1H, C=C**H$_2$**), 5.02 (s, 0.22 × 1H, C**H**=COH, enol), 4.34 (s, 2H, C**H$_2$**OTBDPS), 3.71 (s, 3H, CO_2C**H$_3$**), 3.50 (s, 0.78 × 2H, C(O)C**H$_2$**C(O), keto), 1.99–1.85 (m, 2H, C=CHC**H$_2$**CH_2), 1.60–1.49 (m, 2H, C**H$_2$**CH_2),

[6] Lee, H.; Kim, B.; Snapper, M.; *Org. Lett.* **2003**, *5*, 1855.

1.13 (s, 0.78 × 6H, C(C**H**$_3$)$_2$), 1.07 (s, 9H, SiC(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 168.2, 144.2, 135.6, 134.9, 133.7, 130.2, 129.8, 128.9, 127.8, 113.0, 63.6, 52.4, 48.2, 44.1, 39.3, 28.3, 26.9, 24.1, 19.4; IR (thin film) 2932, 1751, 1708, 1428, 1112, 821, 702 cm^{-1}; HRMS (FAB+) *m/z* = 493.2769 calcd for $C_{30}H_{41}O_4Si$ $[MH]^+$, found 493.2767.

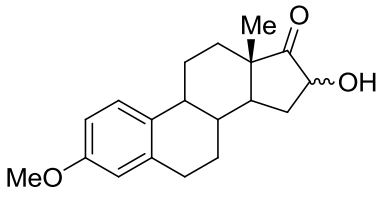


80:20, keto/enol

(*E*)-Methyl 5,5-dimethyl-3-oxoundeca-8,10-dienoate: To a solution of LDA [freshly prepared from diisopropylamine (0.45 mL, 3.21 mmol) and *n*-BuLi (2.5M in hexane, 1.18 mL, 3.21 mmol) in THF (7.5 mL) at -78 °C] was added (*E*)-4,4-dimethylnona-6,8-dien-2-one[7] (0.498 g, 2.67 mmol) in THF (2.5 mL) with stirring. Reaction was allowed to warm to 0 °C over 30 min then cooled again to -78 °C. HMPA (0.46 mL, 2.67 mmol) was added followed by methyl cyanoformate (0.25 mL, 3.21 mmol). Reaction mixture was stirred for 20 min at -78 °C then quenched by addition of water (10 mL). Reaction mixture was extracted with ether (15 mL x 3). Combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (9:1 hexanes/EtOAc) to afford the title compound (0.185 g, 31% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 0.20 × 1H, CH=CO**H,** enol), 6.28 (dt, *J* = 10.2, 17.4 Hz, 1H, CH=CHC**H**=CH_2), 6.01 (dd, *J* = 10.2, 15.0 Hz, 1H, CH=C**H**CH=CH_2), 5.74–5.59 (m, 1H, CH_2C**H**=CH), 5.08 (d, *J* = 16.8 Hz, 1H, CH=C**H$_2$**), 4.96 (d, *J* = 10.2 Hz, 1H, CH=C**H$_2$**), 4.92 (s, 0.20 × 1H, C**H**=COH,

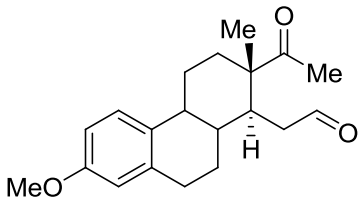
[7] Seyferth, D.; Pornet, J. *J. Org. Chem.* **1980**, *45*, 1721.

enol), 3.70 (s, 3H, $CO_2C\mathbf{H_3}$), 3.38 (s, 0.80 × 2H, $C(O)C\mathbf{H_2}C(O)$, keto), 2.38 (s, 0.80 × 2H, $CC\mathbf{H_2}C{=}O$, keto), 2.10 (d, J = 7.4 Hz, 0.80 × 2H, $C{=}CHC\mathbf{H_2}$, keto), 2.07–2.02 (m, 0.20 × 2H, $C{=}C(CH_3)C\mathbf{H_2}$, enol), 0.99 (s, 0.80 × 6H, $C(C\mathbf{H_3})_2$, keto), 0.94 (s, 0.20 × 6H, $C(C\mathbf{H_3})_2$, enol); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 177.5 (enol), 173.0 (enol), 167.6, 137.1, 134.2, 131.0, 115.6, 91.3 (enol), 52.6, 52.3, 51.0, 46.9, 45.6 (enol), 44.8, 34.4, 27.3; IR (thin film) 2956, 1751, 1717, 1650, 1628, 1448, 1317, 1242, 1006, 900 cm^{-1}; HRMS (FAB+) m/z = 225.1485 calcd for $C_{13}H_{21}O_3$ $[MH]^+$, found 225.1502.



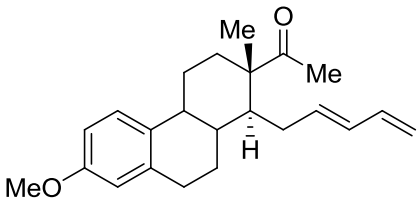
16-Hydroxyestrone methyl ether: To a solution of LDA [freshly prepared from diisopropylamine (2.6 mL, 18.2 mmol) and *n*-BuLi (2.3M in hexane, 7.9 mL, 18.2 mmol) in THF (75 mL) at -78 °C] was added estrone methyl ether (4.71 g, 16.6 mmol) in THF (25 mL) over 5 min. The mixture was stirred at -78 °C for 20 min. then TMSCl (2.3 mL, 18.2 mmol) was added dropwise. The reaction mixture was stirred for an additional 30 min. then warmed to room temperature over 1 h. Saturated $NaHCO_3$ solution (50 mL) was added and the reaction mixture was extracted with pentanes (50 mL × 5). Combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude silyl-enol ether product was then dissolved in CH_2Cl_2 (150 mL) and solid $NaHCO_3$ (11.6 g, 138 mmol) was added. The reaction mixture was cooled to -30 °C and mCPBA (3.42 g, 19.9 mmol) was added with stirring. Reaction was allowed to warm to room temperature over 1 h. Pentanes (320 mL) was then added and the mixture

was filtered through a course fritted funnel and concentrated *in vacuo*. The concentrate was then dissolved in THF (100 mL), cooled to 0 °C, and TBAF (1.0M in THF, 33.1 mL, 33.1 mmol) was added. The mixture was stirred for 1 h and then saturated $NaHCO_3$ solution (50 mL) was added and then extracted with CH_2Cl_2 (75ml × 3). The combined organic layers were washed with brine (75 mL), dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (35% EtOAc in hexanes) to give the title compound as a white solid (3.06 g, 10.2 mmol, 62% yield overall). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.4 Hz, 1H, Ar**H**), 6.72 (dd, *J* = 2.8, 8.6 Hz, 1H, Ar**H**), 6.65 (d, *J* = 2.7 Hz, 1H, Ar**H**), 4.43 (dd, *J* = 2.1, 8.0 Hz, 1H, C**H$_2$**OH), 3.78 (s, 3H, OC**H$_3$**), 2.89 (dd, *J* = 3.8, 8.5 Hz, 2H, ArC**H$_2$**), 2.44–2.35 (m, 1H), 2.31–2.22 (m, 1H), 2.14–1.90 (m, 4H), 1.76 (dt, *J* = 7.1, 10.8 Hz, 1H), 1.66–1.36 (m, 4H), 1.00 (s, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.4, 157.8, 137.8, 131.9, 126.4, 114.0, 111.8, 71.5, 55.4, 48.0, 47.5, 44.0, 38.4, 31.5, 30.5, 29.7, 26.4, 25.7, 14.3; IR (thin film) 3367, 2931, 1744, 1608, 1497, 1451, 1256, 1160, 1095, 1048, 699, 665 cm^{-1}; HRMS (FAB+) *m/z* = 300.1725 calcd for $C_{19}H_{24}O_3$ $[M]^+$, found 300.1738.



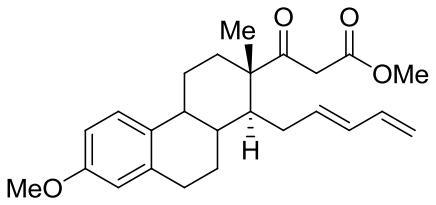
Estrone derived ketone-aldehyde: 16-Hydroxyestrone methyl ether (3.06g, 10.2 mmol) was dissolved in ether (60 mL) and cooled to -78 °C. Methylmagnesium chloride solution (3.0 M in THF, 8.5 mL, 25.5 mmol) was added dropwise with stirring. Reaction

mixture was warmed to room temperature over 30 min then refluxed for 1 h. The reaction mixture was allowed to cool to room temperature and then quenched by addition of saturated NH_4Cl solution (40 mL). The mixture was then extracted with ether (50 mL x 3). The organic layers were combined, washed with brine (50 mL) and concentrated *in vacuo*. The crude residue was then dissolved in THF (50 mL). pH 7 Buffer solution (50 mL) was then added followed by $NaIO_4$ (18.0g, 84.1 mmol). The reaction mixture was stirred for 1 h upon which water (50 mL) was added and the mixture was extracted with ether (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 EtOAc/hexanes) to provide the title compound as a colorless oil (1.31 g, 50% yield overall). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81-9.78 (m, 1H, C**H**O) 7.19 (d, *J* = 8.7 Hz, 1H, Ar**H**), 6.72 (dd, *J* = 2.8, 8.6 Hz, 1H, Ar**H**), 6.62 (d, *J* = 2.8 Hz, 1H, Ar**H**), 3.77 (s, 3H, OC**H$_3$**), 2.85-2.79 (m, 2H, ArC**H$_2$**), 2.62-2.55 (m, 1H), 2.46-2.31 (m, 3H, C(O)C**H$_3$**), 2.18 (s, 3H, C(O)C**H$_3$**), 2.11 (dd, *J* = 2.2, 17.6 Hz, 1H), 1.83-1.77 (m, 2H), 1.76-1.68 (m, 1H), 1.54-1.44 (m, 1H), 1.40-1.30 (m, 2H), 1.14 (s, 3H, C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 157.8, 137.6, 131.5, 126.4, 113.5, 112.0, 55.3, 52.5, 46.2, 42.9, 41.1, 39.0, 35.9, 30.2, 27.5, 25.9, 25.3, 15.2 ; IR (thin film) 3583, 3423, 2936, 1721, 1697, 1610, 1578, 1501, 1453, 1384, 1352, 1282, 1256, 1253, 1156, 1111, 1038, 665 cm^{-1}; HRMS (FAB+) *m/z* = 314.1882 calcd for $C_{20}H_{26}O_3$ $[M]^+$, found 314.1877.



Estrone-derived dienylketone: Allyldiphenylphosphine oxide (1.01 g, 4.17 mmol) was dissolved in THF (15 mL). Hexamethylphosphoramide (0.73 mL, 4.16 mmol) was added with stirring and the reaction mixture was cooled to -78 °C. BuLi (2.5M in hexanes, 1.7 mL, 4.17 mmol) was added dropwise and the reaction was allowed to stir at -78 °C for 30 min. The corresponding estrone-drived ketone-aldehyde (1.31 g, 4.17 mmol) in THF (10 mL) was added dropwise and the reaction mixture and was then allowed to warm to room temperature over 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) and then extracted with ether (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (7.5% EtOAc/hexanes) to furnish the diene (170 mg, 11% yield, 3.5:1 *trans/cis*) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.9 Hz, 1H, Ar**H**), 6.73 (dd, *J* = 2.7, 8.6 Hz, 1H, Ar**H**), 6.64 (d, *J* = 2.4 Hz, 1H, Ar**H**), 6.29 (dt, *J* = 10.2, 17.0 Hz, 1H, CH=CHC**H**=CH_2), 6.03 (dd, *J* = 10.2, 15.1 Hz, 1H, CH=C**H**CH=CH_2), 5.66 (dt, *J* = 7.2, 14.6 Hz, 1H, CH_2C**H**=CH), 5.10 (d, *J* = 16.5 Hz, 1H, CH=C**H$_2$**), 4.98 (d, J = 10.2 Hz, 1H, CH=C**H$_2$**), 3.78 (s, 3H, OC**H$_3$**), 2.92-2.80 (m, 2H, ArC**H$_2$**), 2.44-2.26 (m, 2H), 2.26-2.10 (m, 4H, C(O)C**H$_3$**), 2.10-1.98 (m, 1H), 1.98-1.84 (m, 1H), 1.83-1.60 (m, 2H), 1.54-1.26 (m, 4H), 1.16 (s, 3H, C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8,157.7, 137.9, 137.1, 135.4, 132.2, 131.8, 126.4, 115.3, 113.5, 111.8, 55.3, 52.8, 45.4, 43.0, 41.3, 36.9, 34.4, 30.3, 27.3, 25.9, 25.8, 15.3; IR (thin

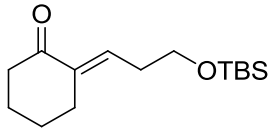
film) 3378, 2932, 2862, 2835, 1698, 1610, 1501, 1465, 1432, 1352, 1282, 1255, 1239, 1156, 1043, 1006, 901, 786, 735, 605 cm^{-1}; HRMS (FAB+) *m/z* = 338.2246 calcd for $C_{20}H_{26}O_3$ $[M]^+$, found 338.2236.



82:18, keto/enol

Estrone-derived dienyl-β-ketoester: To a solution of LDA [freshly prepared from diisopropylamine (87 μL, 0.617 mmol) and *n*-BuLi (2.5M in hexane, 226 μL, 0.565 mmol) in THF (1.5 mL) at -78 °C] was added the estrone-derived dienylketone (174 mg, 0.514 mmol) in THF (0.5 mL) with stirring. The reaction mixture was allowed to warm to 0 °C over 1 h then cooled again to -78 °C. HMPA (89 μL, 0.514 mmol) was added followed by methyl cyanoformate (49 μL, 0.617 mmol). Reaction was stirred for 20 min at -78 °C then quenched by addition of water (2 mL). Reaction mixture was extracted with ether (2 mL x 3). Combined organic layers were washed with brine (2 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (9:1 hexanes/EtOAc) to afford the title compound (47.7 mg, 23% yield, 3.5:1 *trans/cis*) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (s, 0.18 × 1H, CH=CO**H**, enol), 7.18 (d, *J* = 9.2 Hz, 1H, Ar**H**), 6.72 (dd, *J* = 2.9, 8.7 Hz, 1H, Ar**H**), 6.63 (d, *J* = 2.6 Hz, 1H, Ar**H**), 6.30 (dt, *J* = 10.4, 16.8 Hz, 1H, CH=CHC**H**=CH_2), 6.10–5.90 (m, 1H, CH=C**H**CH=CH_2), 5.65 (dt, *J* = 7.4, 14.2 Hz, 1H, CH_2C**H**=CH), 5.17 (s, 0.18 × 1H, enol), 5.10 (d, *J* = 17.0 Hz, 1H, CH=C**H$_2$**), 4.99 (d, *J* = 10.1 Hz, 1H, CH=C**H$_2$**), 3.78

(s, 3H, ArOC**H$_3$**), 3.74 (s, 3H, CO_2C**H$_3$**), 3.60–3.53 (m, 0.82 × 2H, C(O)C**H$_2$**C(O), keto), 2.88–2.80 (m, 2H, ArC**H$_2$**), 2.46–1.87 (m, 6H), 1.78–1.68 (m, 2H), 1.52-1.31 (m, 3H), 1.18 (s, 0.82 × 3H, C**H$_3$**, keto), 1.06 (s, 0.18 × 3H, C**H$_3$**, enol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 168.4, 157.8, 138.0, 137.2, 135.0, 132.2, 132.0, 126.5, 115.5, 113.6, 111.9, 55.4, 53.5, 52.4, 45.3, 44.7, 43.0, 41.3, 36.8, 34.5, 30.3, 27.3, 25.8, 15.1; IR (thin film) 3427, 2933, 1748, 1701, 1611, 1501, 1434, 1317, 1255, 1239, 1154, 1044, 1005 cm^{-1}; HRMS (FAB+) *m/z* = 396.2295 calcd for $C_{25}H_{31}O_4$ $[M]^+$, found 396.2313.

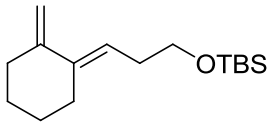


(*E*)-2-(3-(*tert*-Butyldimethylsilyloxy)propylidene)cyclohexanone: To a solution of LDA [freshly prepared from diisopropylamine (10.8 mL, 76.5 mmol) and *n*-BuLi (2.5M in hexane, 30.0 mL, 74.8 mmol) in THF (300 mL) at -78 °C] was added cyclohexanone (6.67 g, 68.0 mmol) in THF (50 mL) dropwise at -78 °C. Reaction mixture was stirred for 1 h at -78 °C then 3-(tert-butyldimethylsilyloxy)propanal[8] (6.39 g, 34.0 mmol) in THF (100 mL) was added *via* syringe. The reaction was stirred for 1 h at -78 °C then quenched by addition of saturated NH_4Cl solution (150 mL). The mixture was extracted with ether (200mL × 3). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (4:1, hexanes/EtOAc) to afford the 2-(3-(*tert*-butyldimethylsilyloxy)-1-

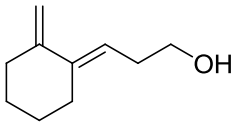
[8] Jenmalm, A.; Berts, W.; Li, Y.; Luthman, K.; Csoeregh, I.; Hacksell, U. *Journal of Organic Chemistry* **1994,** *59*, 1139.

hydroxypropyl)cyclohexanone (7.45g, 26.0 mmol, 76% yield) as a colorless oil that was used immediately.

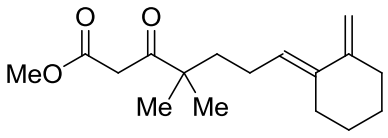
2-(3-(*tert*-Butyldimethylsilyloxy)-1-hydroxypropyl)cyclohexanone (7.45 g, 26.0 mmol) was dissolved in CH_2Cl_2 (300 mL). Triethylamine (18.1 mL, 130 mmol) was added and the reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (6.26 mL, 80.6 mmol) was added dropwise with stirring. Stirring was continued for 3 h while the reaction was allowed to warm to room temperature. Water (200 mL) was added and the reaction mixture was extracted with ether (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude mesylate was then dissolved in THF (200 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (8.16 mL, 54.6 mmol) was added. The mixture was stirred for 1 h at room temperature then diluted with ether (500 mL) and washed with water (200 mL), 1N HCl solution (200 mL), and then with brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (9:1, hexanes/EtOAc) to afford the title compound (3.69 g, 13.7 mmol, 53% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57–6.50 (m, 1H, C=C**H**CH_2), 3.65 (t, *J* = 7.0 Hz, 2H, C**H$_2$**OTBS), 2.46 (t, *J* = 5.9 Hz, 2H, CH_2C**H$_2$**CO), 2.35 (t, *J* = 6.8 Hz, 2H, C**H$_2$**C=C), 2.27 (dt, *J* = 6.7, 7.6 Hz, 2H, HC=CC**H$_2$**), 1.83–1.75 (m, 2H, C**H$_2$**CH_2), 1.73–1.65 (m, 2H, CH_2C**H$_2$**), 0.83 (s, 9H, SiC(C**H$_3$**)$_3$), 0.01 (s, 6H, Si(C**H$_2$**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 137.7, 135.4, 61.8, 40.1, 31.6, 26.8, 25.9, 23.6, 23.4, 18.3, -5.3; IR (thin film) 2953, 2930, 2858, 1716, 1472, 1255, 1099, 837, 778 cm^{-1}; HRMS (FAB+) *m/z* = 269.1931 calcd for $C_{15}H_{27}O_{2Si}$ $[MH]^+$, found 269.1948.



(*E*)-*tert*-Butyldimethyl(3-(2-methylenecyclohexylidene)propoxy)silane: To a suspension of methyltriphenylphosphonium bromide (3.34g, 9.34 mmol) in THF (10 mL) at -78 °C was added butyl lithium (2.5M in hexanes, 3.57 mL, 8.92 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C and then stirred for an additional 1 h. The reaction mixture was cooled to -78 °C and a solution of (E)-2-(3-(tert-Butyldimethylsilyloxy)propylidene)cyclohexanone (2.28g, 8.49 mmol) in THF (45 mL) was added dropwise. The reaction mixture was allowed to warm to 0 °C and stirring was continued for 3 h. Reaction mixture was quenched by addition of saturated NH_4Cl solution (50 mL) and extracted with ether (75 mL × 3). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (40:1, hexanes/EtOAc) to provide the title compound (2.08 g, 7.82 mmol, 92% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (t, J = 7.1 Hz, 1H, C=C**H**CH_2), 4.80 (d, J = 1.6 Hz, 1H, C=C**H$_2$**), 4.56 (d, J = 1.0 Hz, 1H, C=C**H$_2$**), 3.62 (t, J = 6.7 Hz, 2H, C**H$_2$**OTBS), 2.32–2.20 (m, 6H, C=CC**H$_2$**), 1.69–1.56 (m, 4H, C**H$_2$**C**H$_2$**), 0.90 (s, 9H, SiC(C**H$_3$**)$_3$), 0.06 (s, 6H, Si(C**H$_2$**)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 142.1, 119.3, 107.2, 63.2, 35.6, 31.4, 28.8, 27.3, 26.5, 26.1, 18.5, -5.1; IR (thin film) 2928, 2857, 1627, 1472, 1445, 1383, 1255, 939, 888, 837, 775 cm^{-1}; HRMS (FAB+) *m/z* = 267.2139 calcd for $C_{16}H_{31}OSi$ $[MH]^+$, found 267.2147.



(*E*)-3-(2-Methylenecyclohexylidene)propan-1-ol: (E)-*tert*-Butyldimethyl(3-(2-methylenecyclohexylidene)propoxy)silane (2.08 g, 7.82 mmol) was dissolved in THF (100 mL). Tetrabutylammonium fluoride (1.0M in THF, 15.6 mL, 15.6 mmol) was added and reaction was stirred at room temperature for 1 h. Saturated NH_4Cl solution (100 mL) was added and the mixture was extracted with EtOAc (100 mL ×3). The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (4:1, hexanes/EtOAc) to furnish the title compound (0.856 g, 5.62 mmol, 72% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (t, *J* = 7.2 Hz, 1H, C=C**H**CH_2), 4.77 (s, 1H, C=C**H$_2$**), 4.53 (s, 1H, C=C**H$_2$**), 3.58 (t, *J* = 6.6 Hz, 2H, C**H$_2$**OH), 2.27 (dd, *J* = 6.9, 6.9 Hz, 2H, C=CC**H$_2$**), 2.23–2.15 (m, 4H, C=CC**H$_2$**), 1.64–1.50 (m, 4H, C**H$_2$**C**H$_2$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 143.6, 118.5, 107.5, 62.5, 35.6, 31.1, 28.8, 27.2, 26.5; IR (thin film) 3393, 2933, 2863, 1728, 1437, 1274, 1054, 735 cm^{-1}; HRMS (EI+) *m/z* = 152.1196 calcd for $C_{10}H_{16}O$ $[M]^+$, found 152.1210.



73:27, keto/enol

(*E*)-Methyl 4,4-dimethyl-7-(2-methylenecyclohexylidene)-3-oxoheptanoate: To CH_2Cl_2 (50 mL) was added triphenylphosphine (3.23 g, 12.3 mmol), imidazole (0.837g,

12.3 mmol), and iodine (2.76 g, 10.8 mmol). The mixture is then cooled to -10 °C[9] and (E)-3-(2-methylenecyclohexylidene)propan-1-ol (1.38 g, 9.07 mmol) in in THF (2 mL) is added slowly. The reaction mixture was stirred at -10 °C for 1.5 h. The mixture was then diluted with pentane (50 mL) and filtered through a 2" plug of silica with additional pentanes. The solution was then concentrated *in vacuo* to yield the crude iodide (2.14 g, 8.16 mmol, 90% yield) that was used immediately.

To a suspension of NaH (60% in oil, 0.272 g, 6.80 mmol) in THF (40 mL) at 0 °C was added methyl 4-methyl-3-oxovalerate (0.980 g, 6.80 mmol) in THF (2 mL) dropwise. The reaction was stirred for 15 min at 0 °C then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 2.7 mL, 6.8 mmol) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to 0 °C and the above iodide (2.14 g, 8.16 mmol) in THF (2 mL) was added. The reaction was then allowed to stir overnight at 4 °C (cold room). The reaction was quenched by addition of saturated NH_4Cl solution (30 mL) followed by extraction with ether (40 mL × 3). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound (0.912 g, 3.28 mmol, 40% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 0.27 × 1H, CH=CO**H**, enol), 5.34 (t, *J* = 7.3 Hz, 1H, CH_2C**H**=C), 5.01 (s, 0.27 × 1H, C**H**=COH**,** enol), 4.73 (s, 1H, C=C$\mathbf{H_2}$), 4.51 (s, 1H, C=C$\mathbf{H_2}$), 3.69 (s, 3H, $CO_2C\mathbf{H_3}$), 3.50 (s, 0.73 × 2H, C(O)C$\mathbf{H_2}$C(O), keto), 2.20–2.11 (m, 4H, C=CC$\mathbf{H_2}$), 1.94–1.85 (m, 2H, C=CHC$\mathbf{H_2}$), 1.63–1.59 (m, 6H, C$\mathbf{H_2}$C$\mathbf{H_2}$C$\mathbf{H_2}$), 1.13 (s, 0.73 × 6H, C(C$\mathbf{H_3}$)$_2$, keto), 1.10 (s, 0.27 × 6H, enol, C(C$\mathbf{H_3}$)$_2$); ^{13}C NMR (100 MHz,

[9] Conducting the reaction at room temperature leads to a significant amount (~20%) of an inseparable olefin migration isomer.

$CDCl_3$) δ 207.6, 184.8, 168.1, 151.1, 140.8, 140.2, 122.9, 122.2, 107.2, 107.0, 86.8, 52.2, 51.1, 48.2, 44.0, 40.4, 39.8, 35.5, 28.5, 27.1, 26.3, 25.5, 24.0, 22.8, 22.7; IR (thin film) 3393, 2931, 1752, 1708, 1620, 1438, 1305, 1217, 1156, 1052, 887, 665 cm^{-1}; HRMS (FAB+) *m/z* = 278.1876 calcd for $C_{17}H_{26}O_3$ $[M]^+$, found 278.1894.

Addition of product-like molecule experiment – $Pd(OAc)_2$:

$Pd(OAc)_2$ (4.4 mg, 0.020 mmol), $Mg(ClO_4)_2$ (22 mg, 0.10 mmol), and methyl 2-oxobicyclo[4.1.0]heptane-1-carboxylate[10] (17 mg, 0.10 mmol) were dissolved in 1 mL DMSO. (*E*)-Methyl 3-oxoundeca-8,10-dienoate (20 mg, 0.10 mmol) was added, followed finally by copper acetate (46 mg, 0.25 mmol). The vial was then capped, warmed to 65 °C, and stirred for 18 h. The reaction mixture was then diluted with EtOAc to 20 times the volume of the reaction mixture and washed with equivalent volumes of saturated $NaHCO_3$ solution and brine. The organic phase was then dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was then examined directly by ^1H NMR. The vinylcyclopropane product was observed in approximately 20% yield compared to benzyl ether as internal standard.

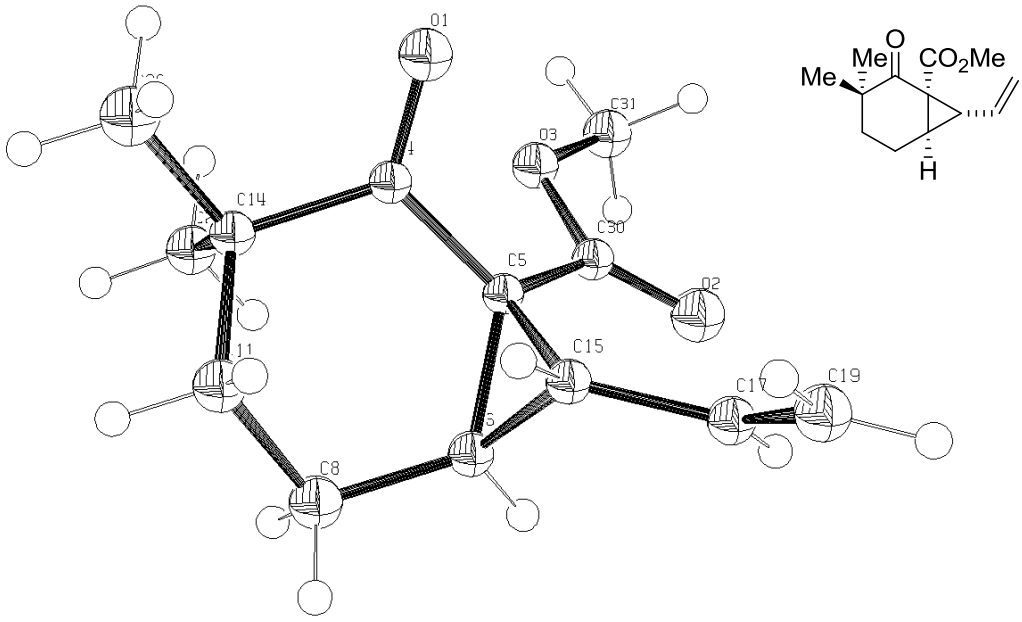
Addition of product-like molecule experiment – Pd_2dba_3:

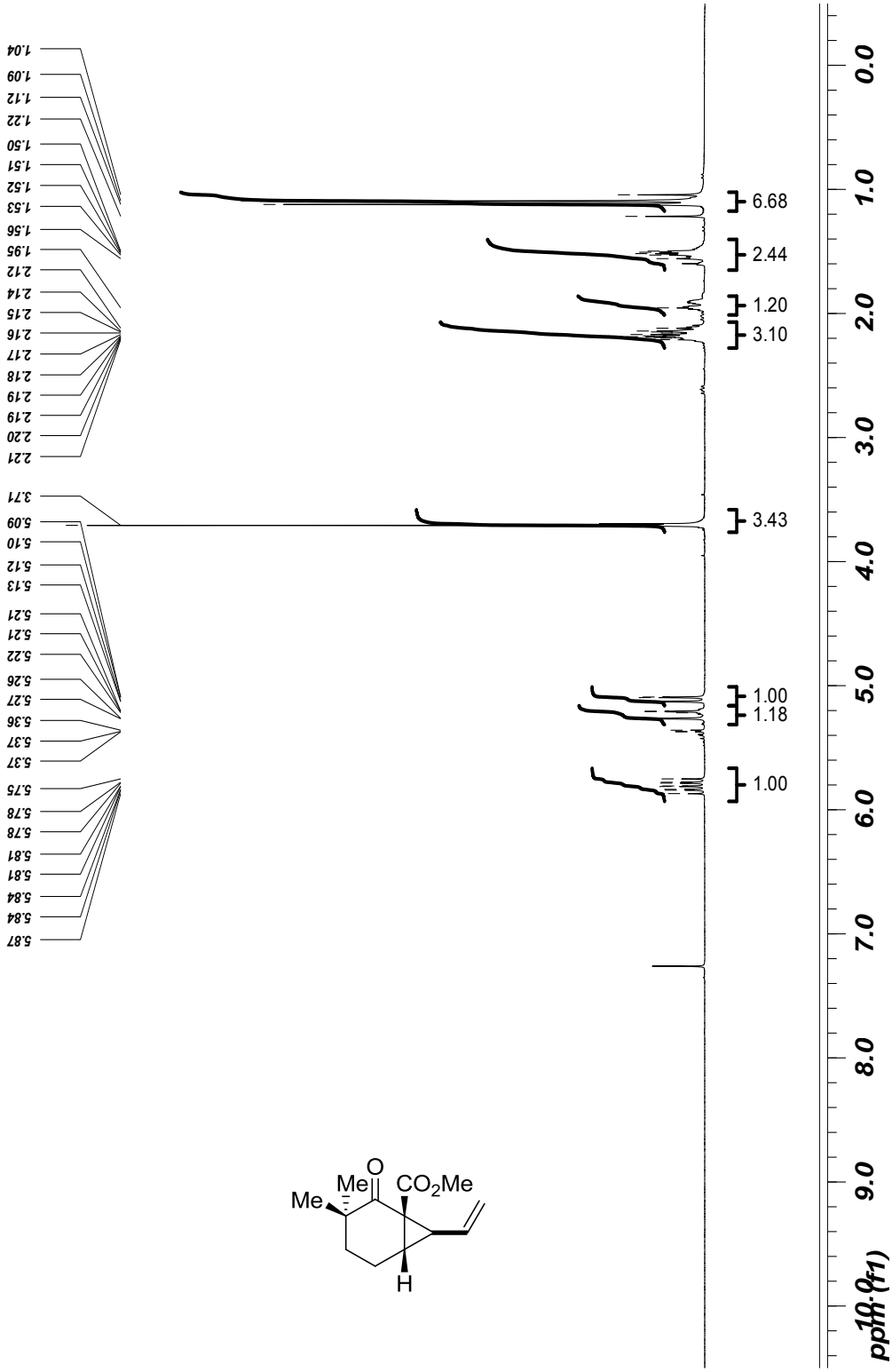
Pd_2dba_3 (9.2 mg, 0.010 mmol), $Mg(ClO_4)_2$ (22 mg, 0.10 mmol), and methyl 2-oxobicyclo[4.1.0]heptane-1-carboxylate (17 mg, 0.10 mmol) were dissolved in 1 mL DMSO. (*E*)-Methyl 3-oxoundeca-8,10-dienoate (20 mg, 0.10 mmol) was added,

[10] Yang, D.; Gao, Q.; Lee, C.-S.; Cheung, K.-K. *Org. Lett.* **2002**, *4*, 3271.

followed finally by copper acetate (46 mg, 0.25 mmol). The vial was then capped, warmed to 65 °C, and stirred for 18 h. The reaction mixture was then diluted with EtOAc to 20 times the volume of the reaction mixture and washed with equivalent volumes of saturated $NaHCO_3$ solution and brine. The organic phase was then dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was then examined directly by ^1H NMR. No vinylcyclopropane product was observed. The vinylcyclopropane product was observed in approximately 20% yield compared to benzyl ether as internal standard in the control (no cyclopropyl-β-ketoester) experiment.

Crystal structure of (±)-(1R,6S,7S)-methyl 3,3-dimethyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate:

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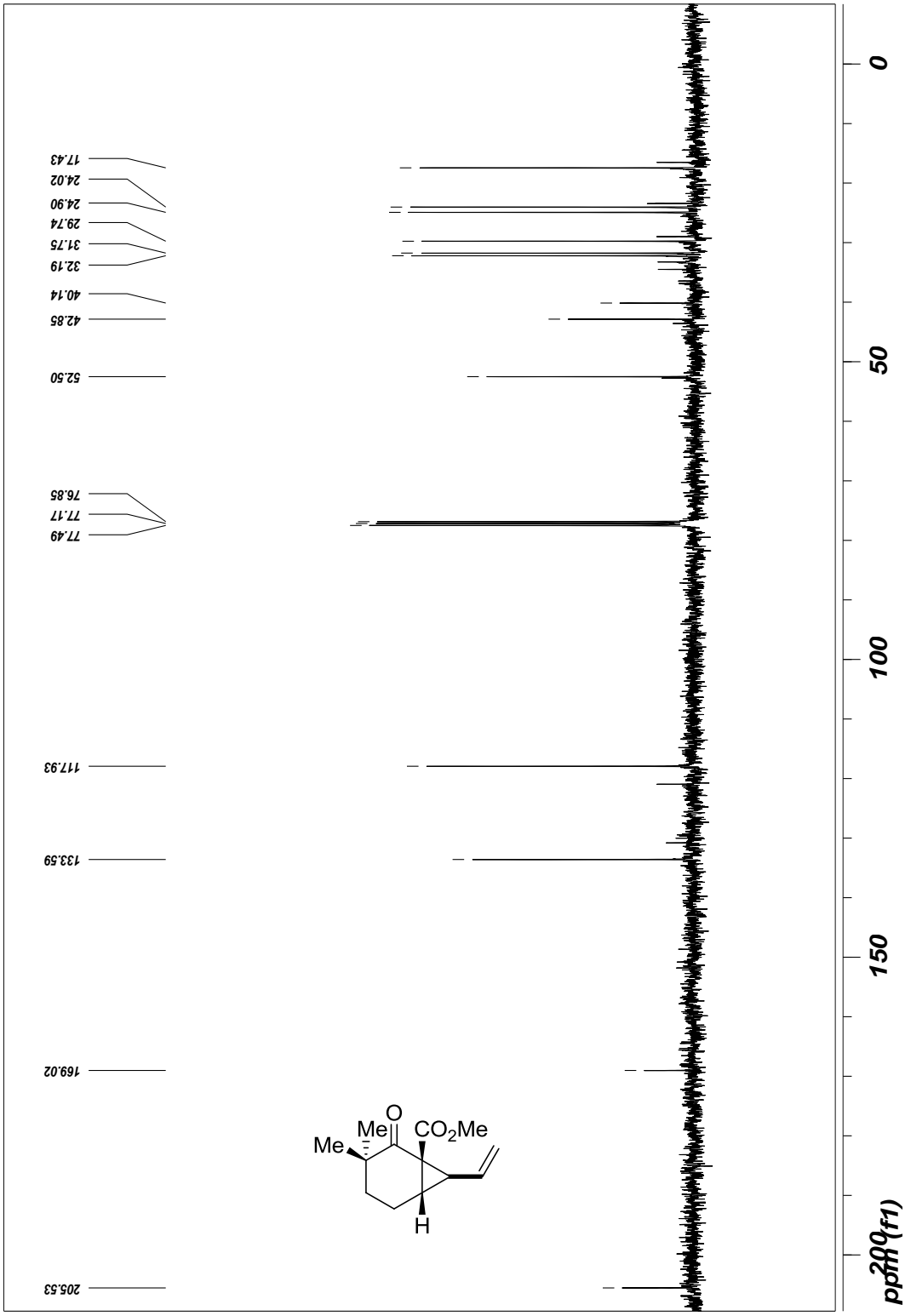
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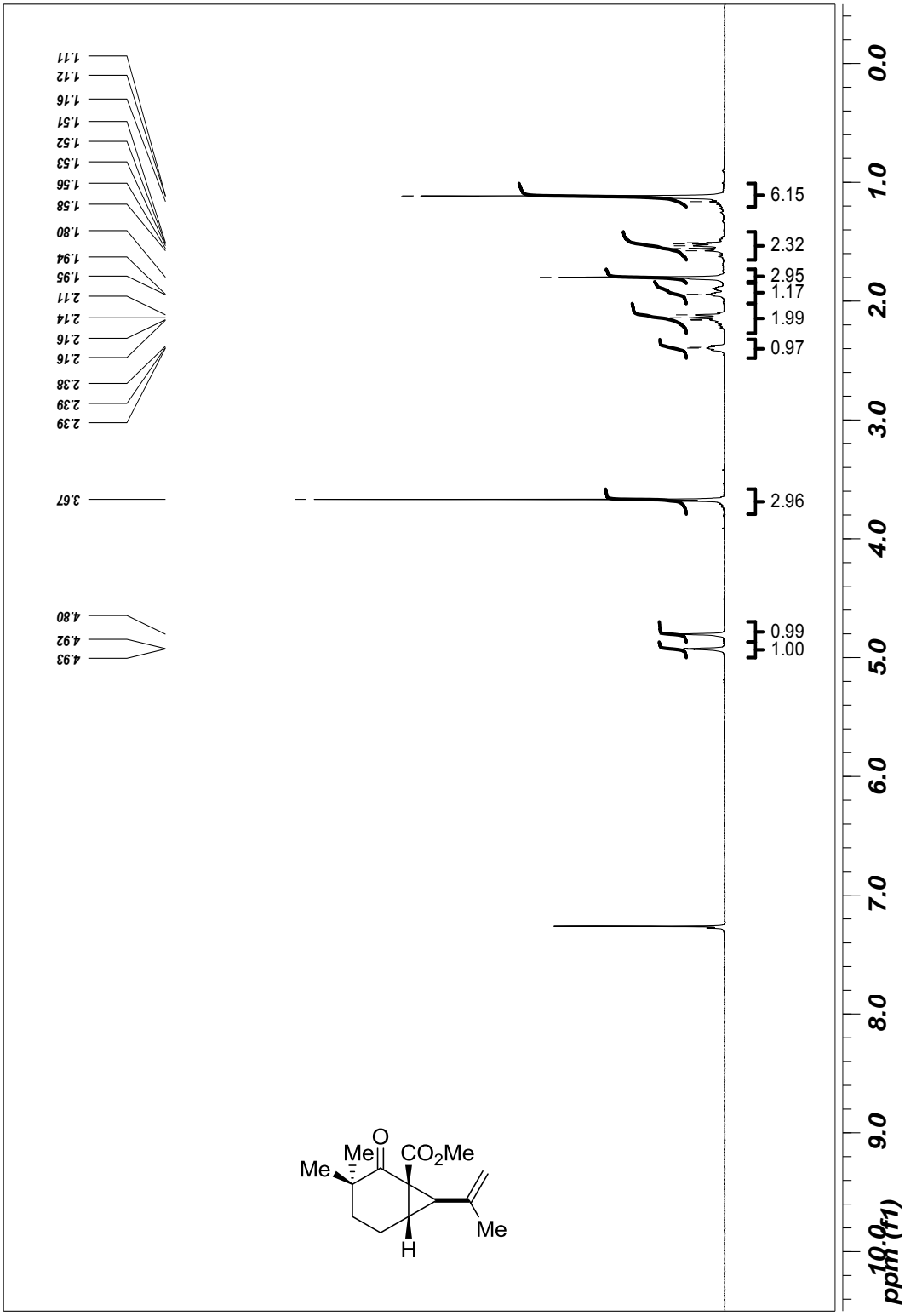
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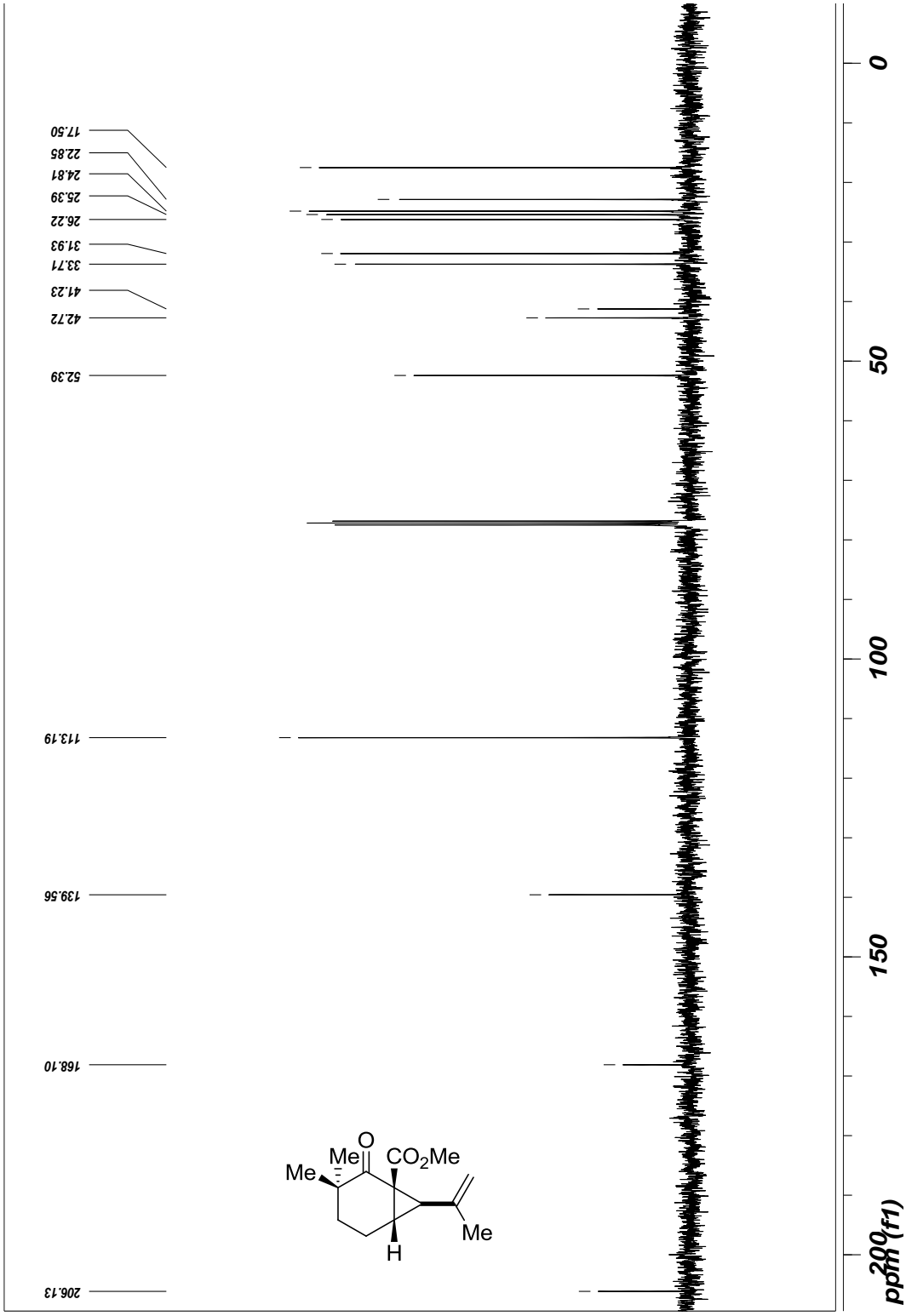
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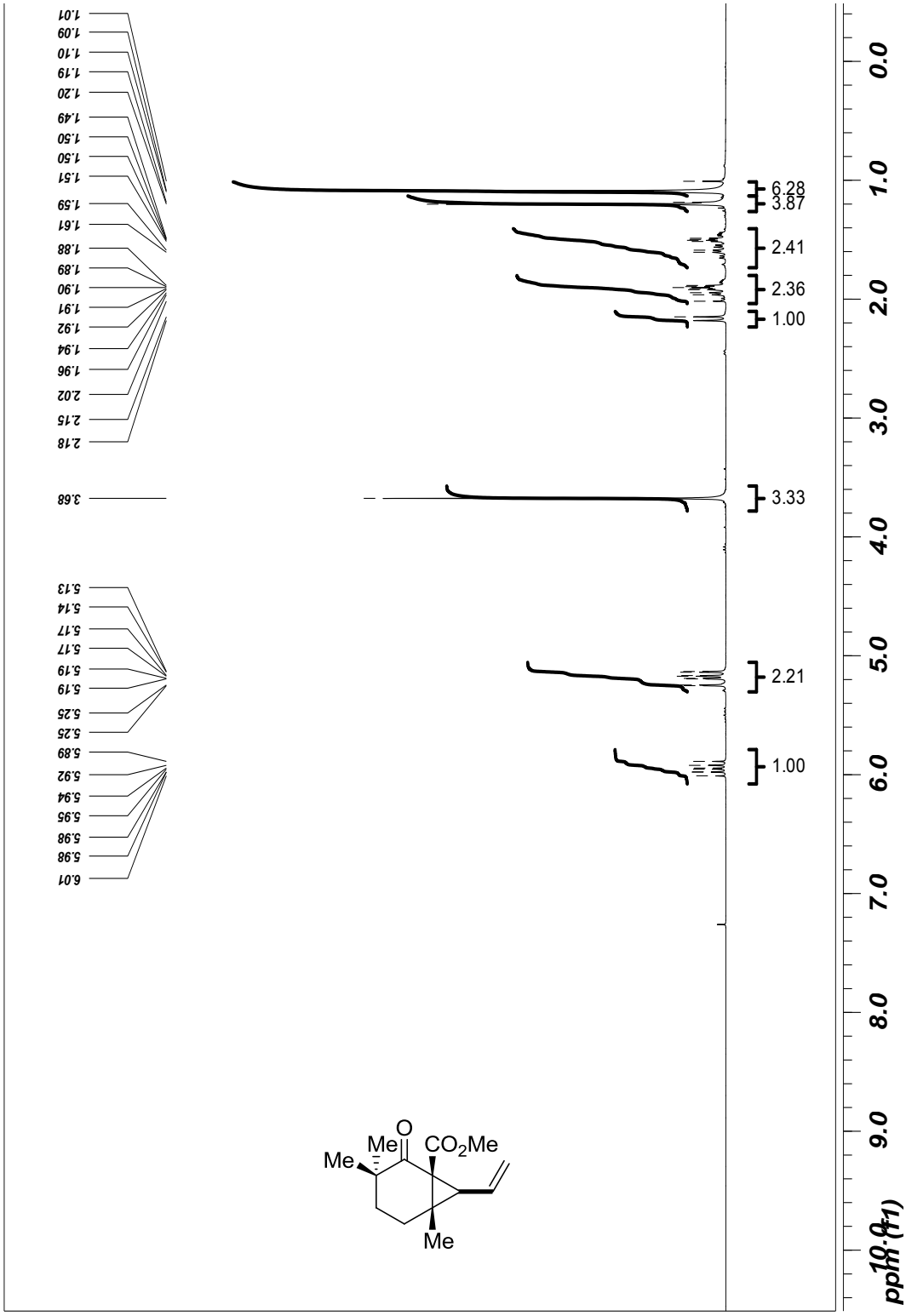
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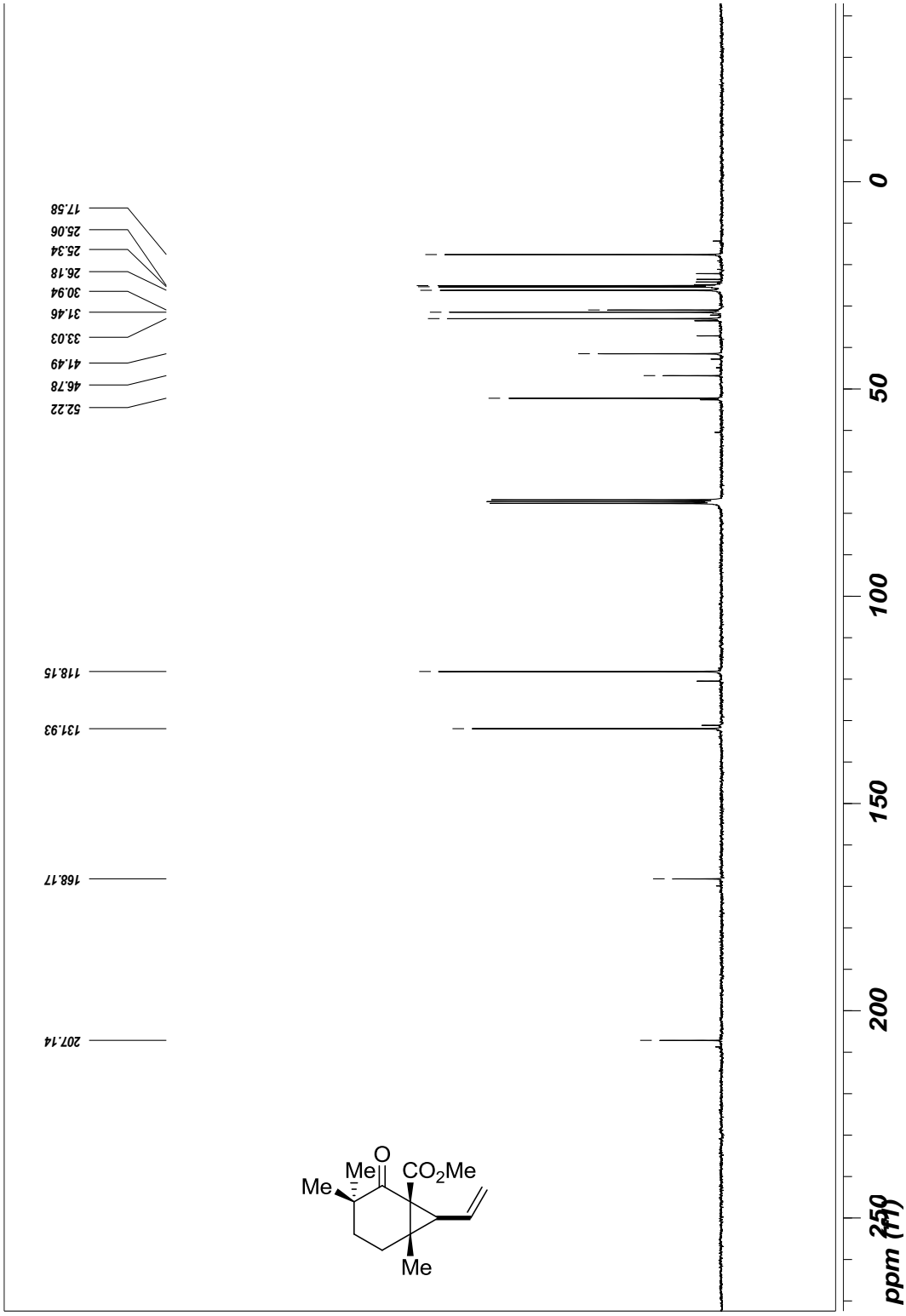
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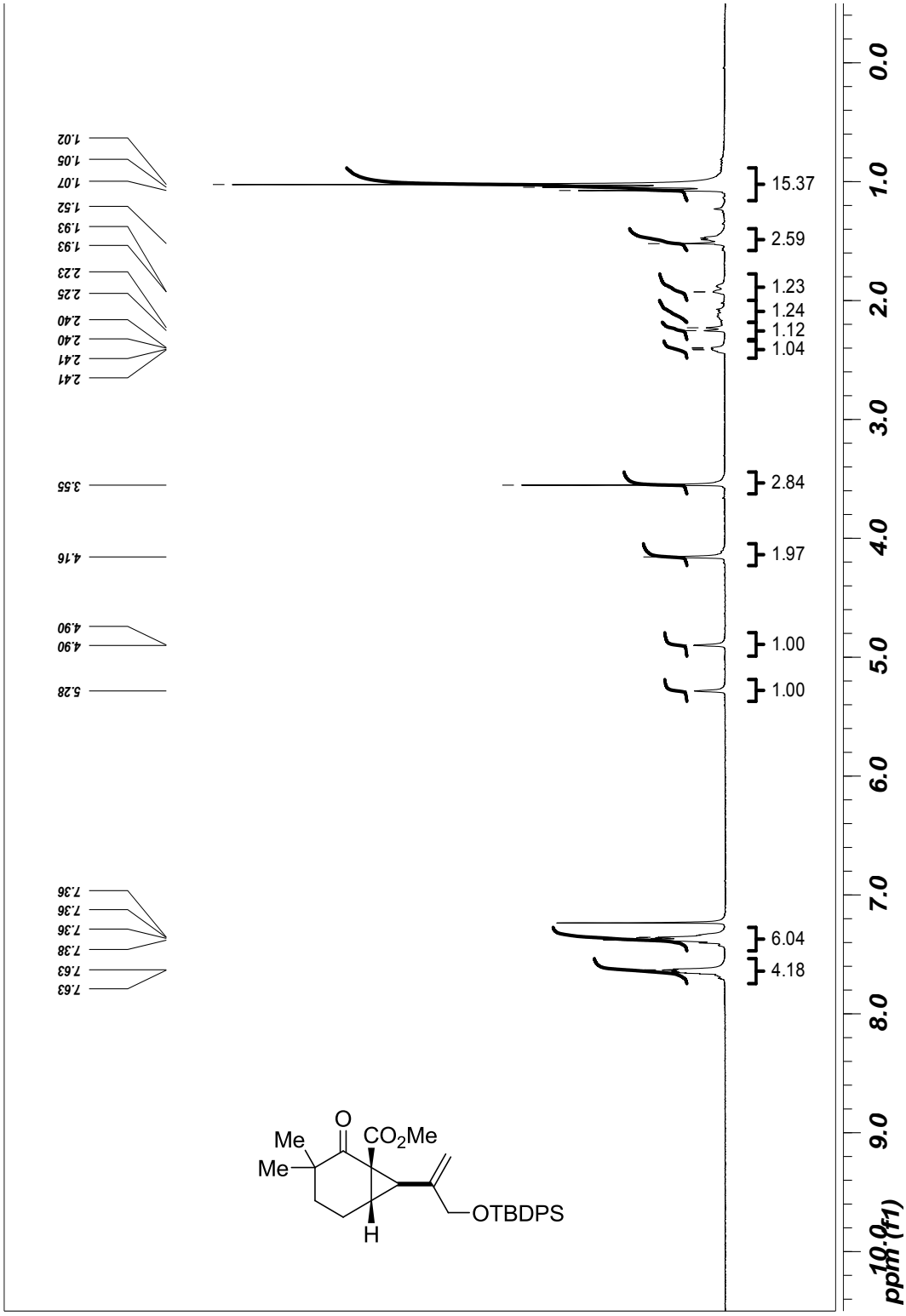
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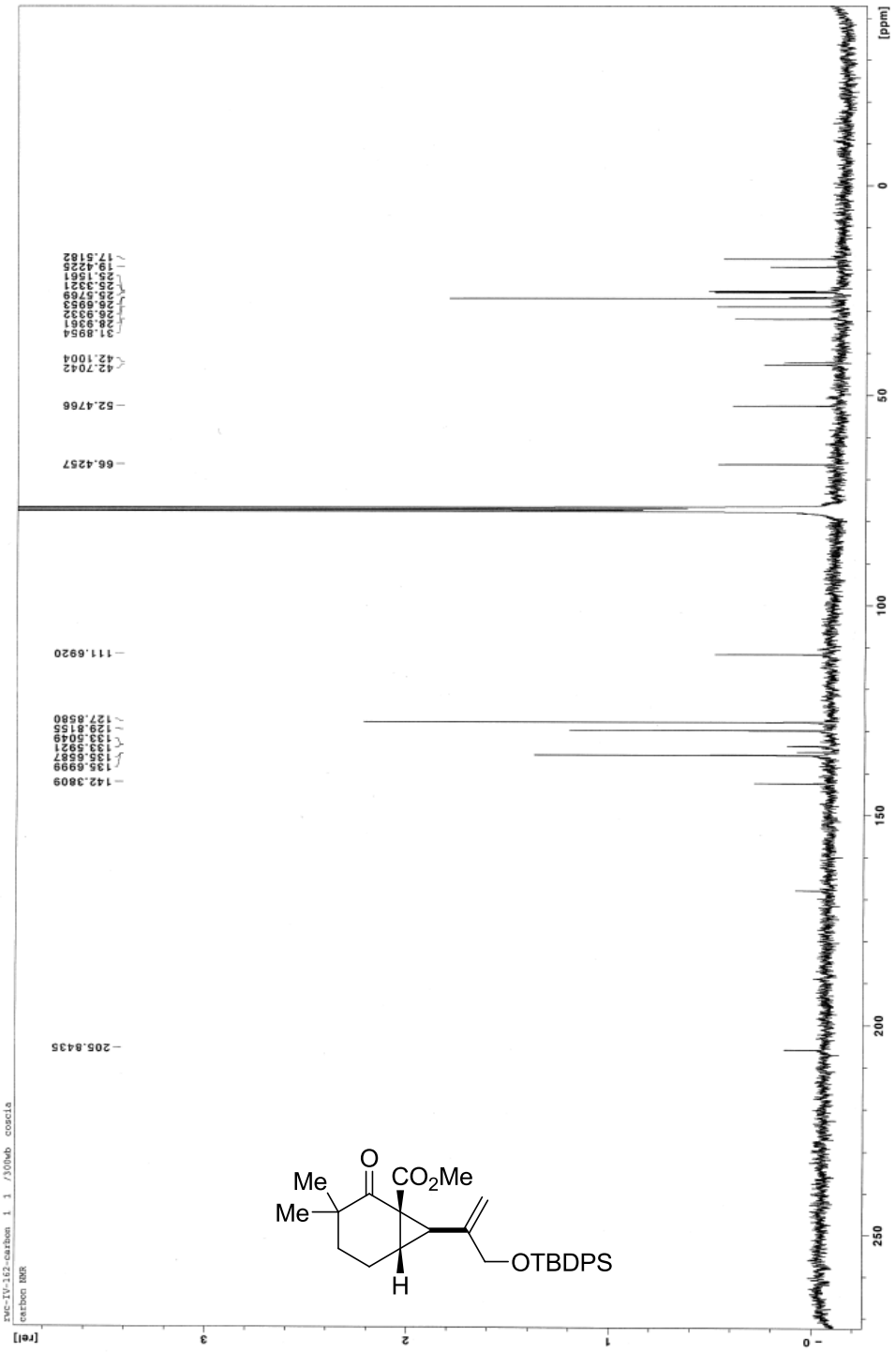
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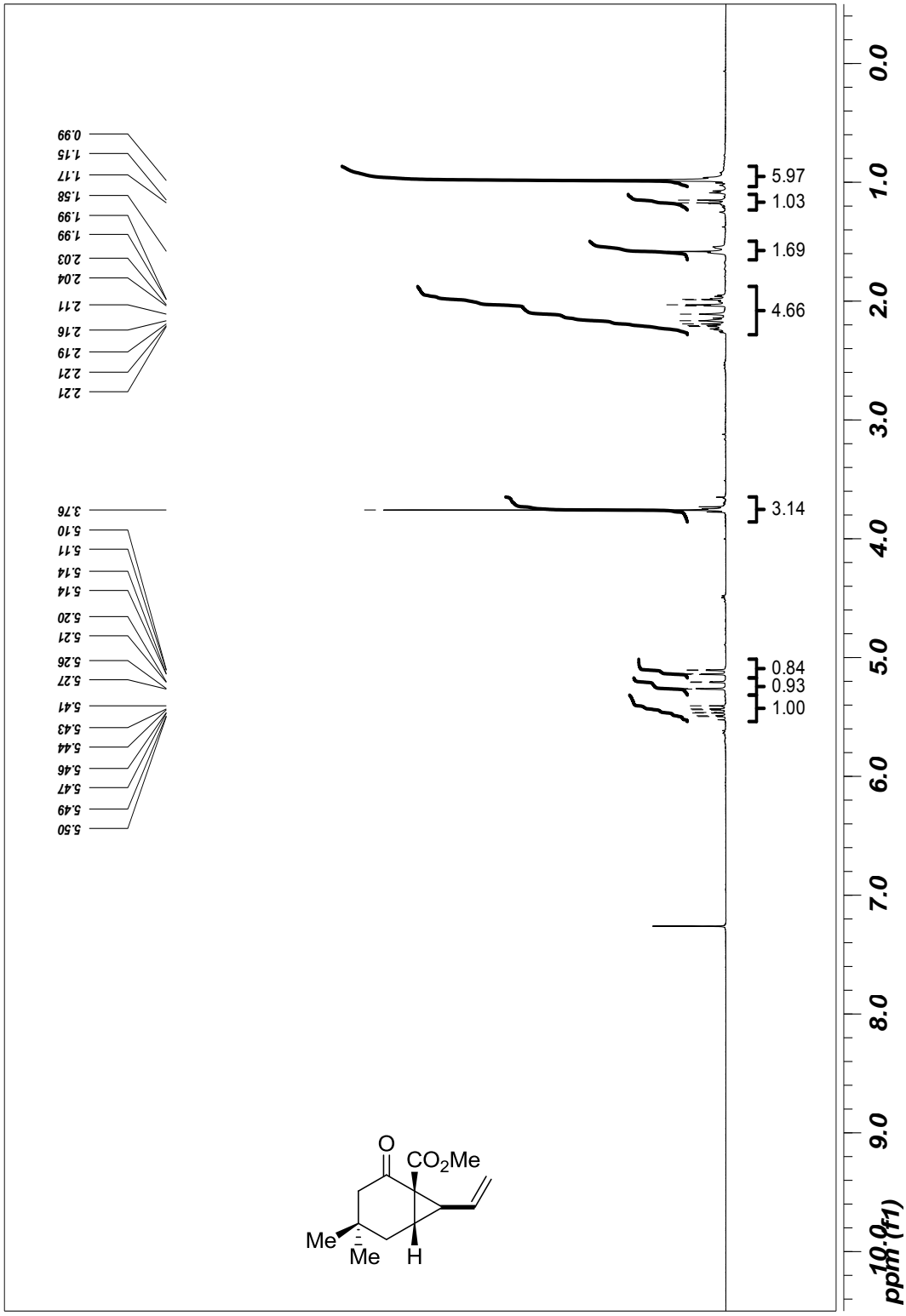
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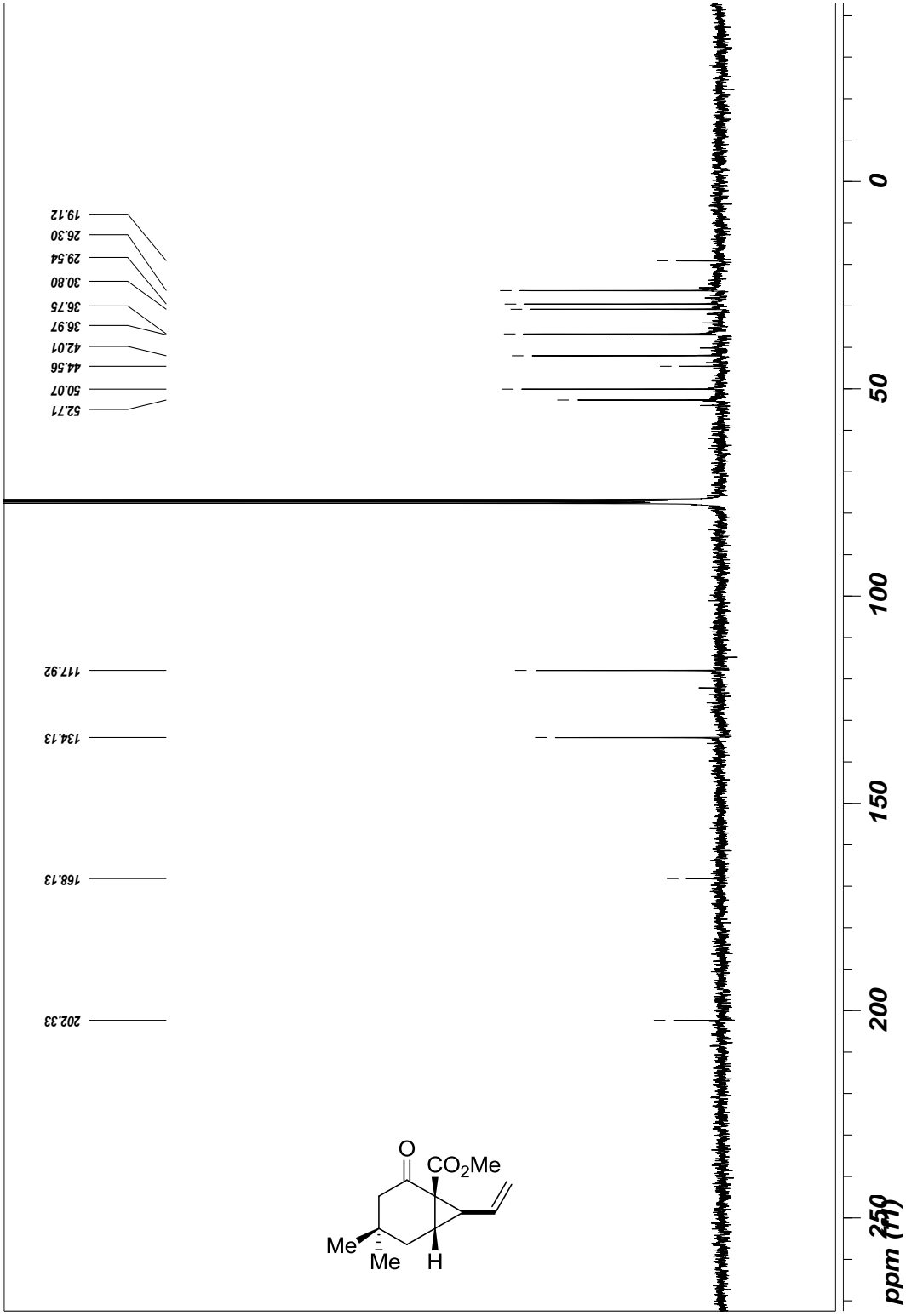
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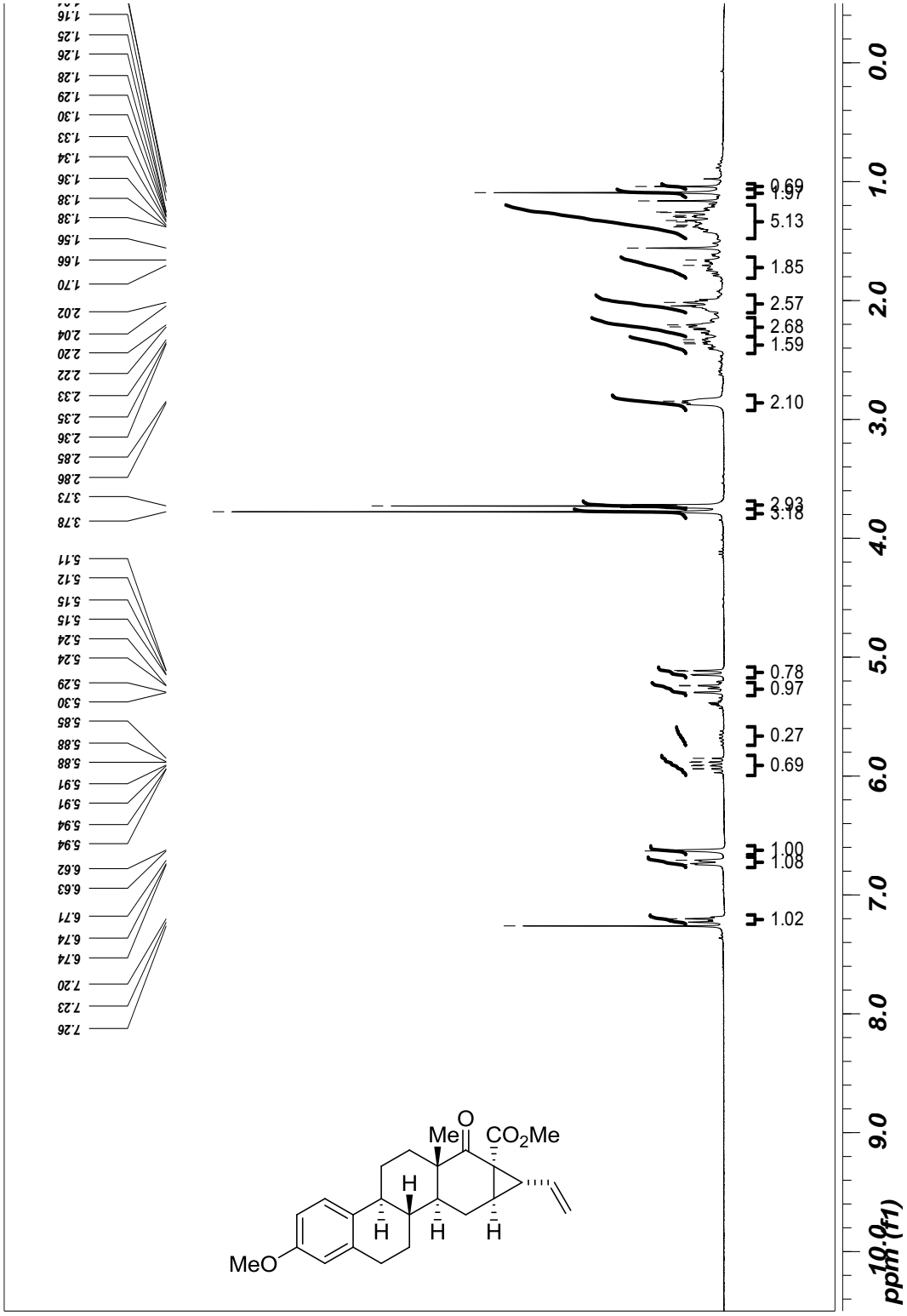
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0.69
1.00
1.08
1.02
0.0
1.0
2.0
3.0
4.0
5.0
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9.0
10.0
ppm (f1)
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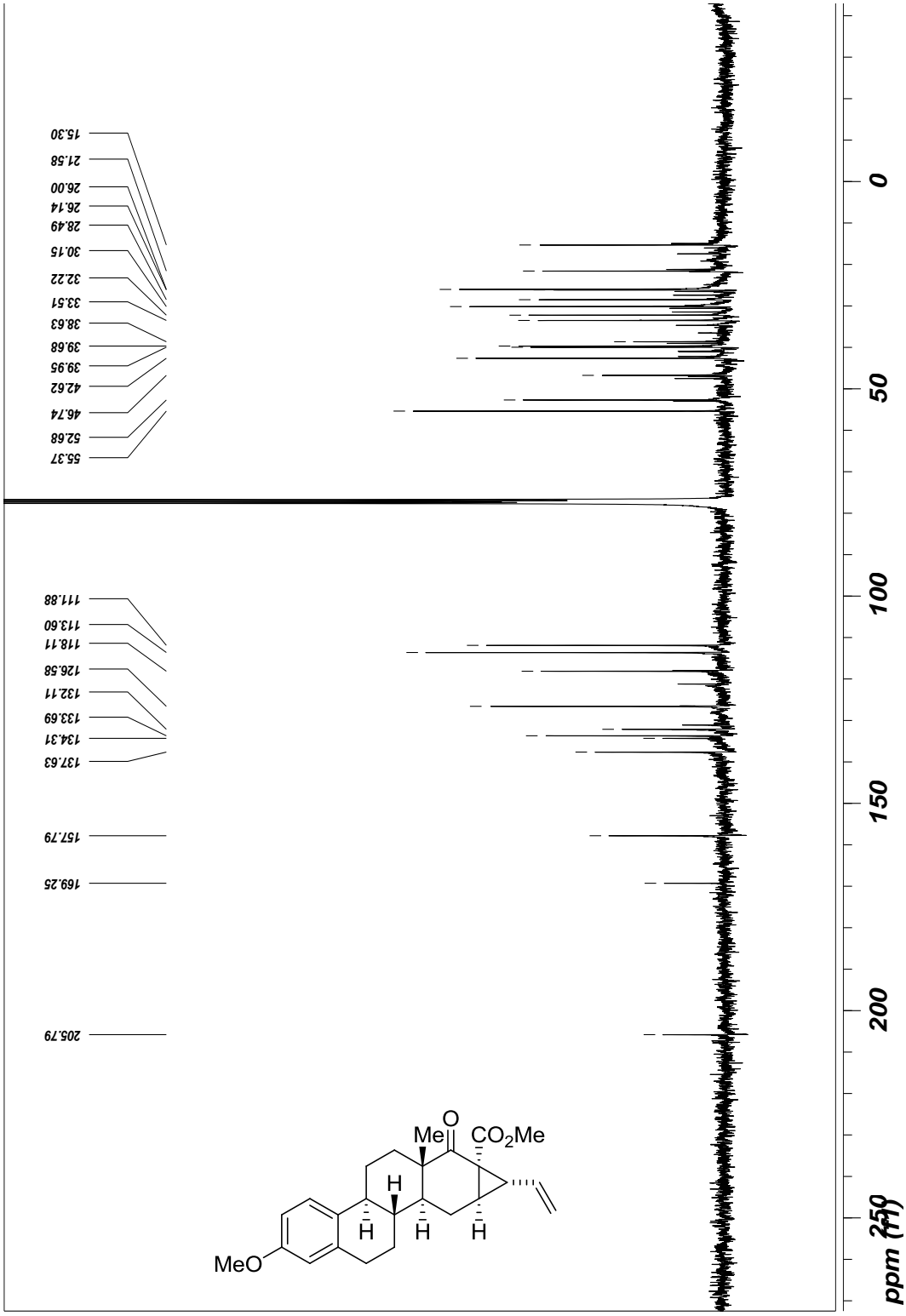
Me
CO2Me
H
H
H
H
MeO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52.68
55.37
111.88
113.60
118.11
126.58
132.11
133.69
134.31
137.63
157.79
169.25
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150
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250
ppm (f1)
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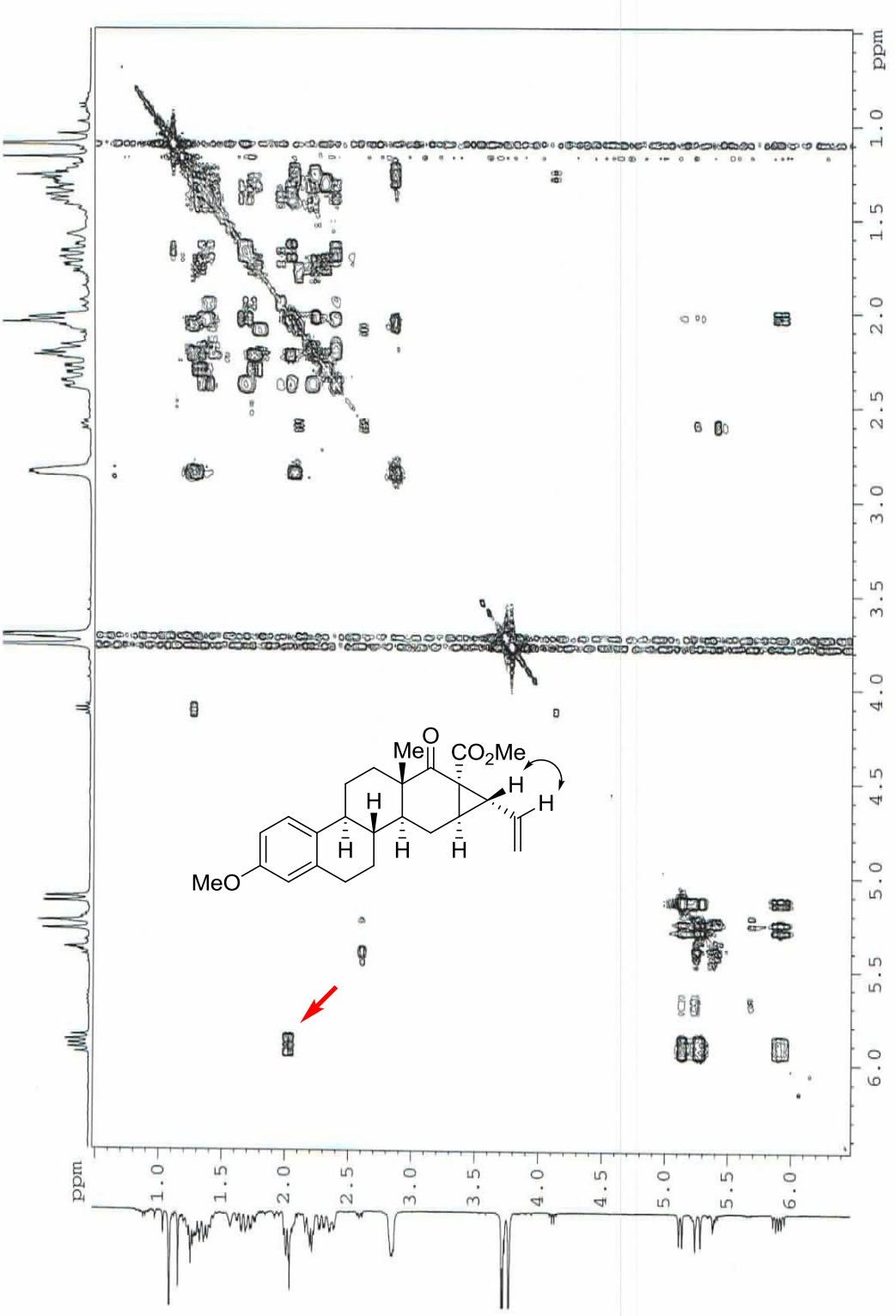
O
CO2Me
H
H
H
H
MeO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CO2Me
H
H
H
H
H
MeO
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4.0
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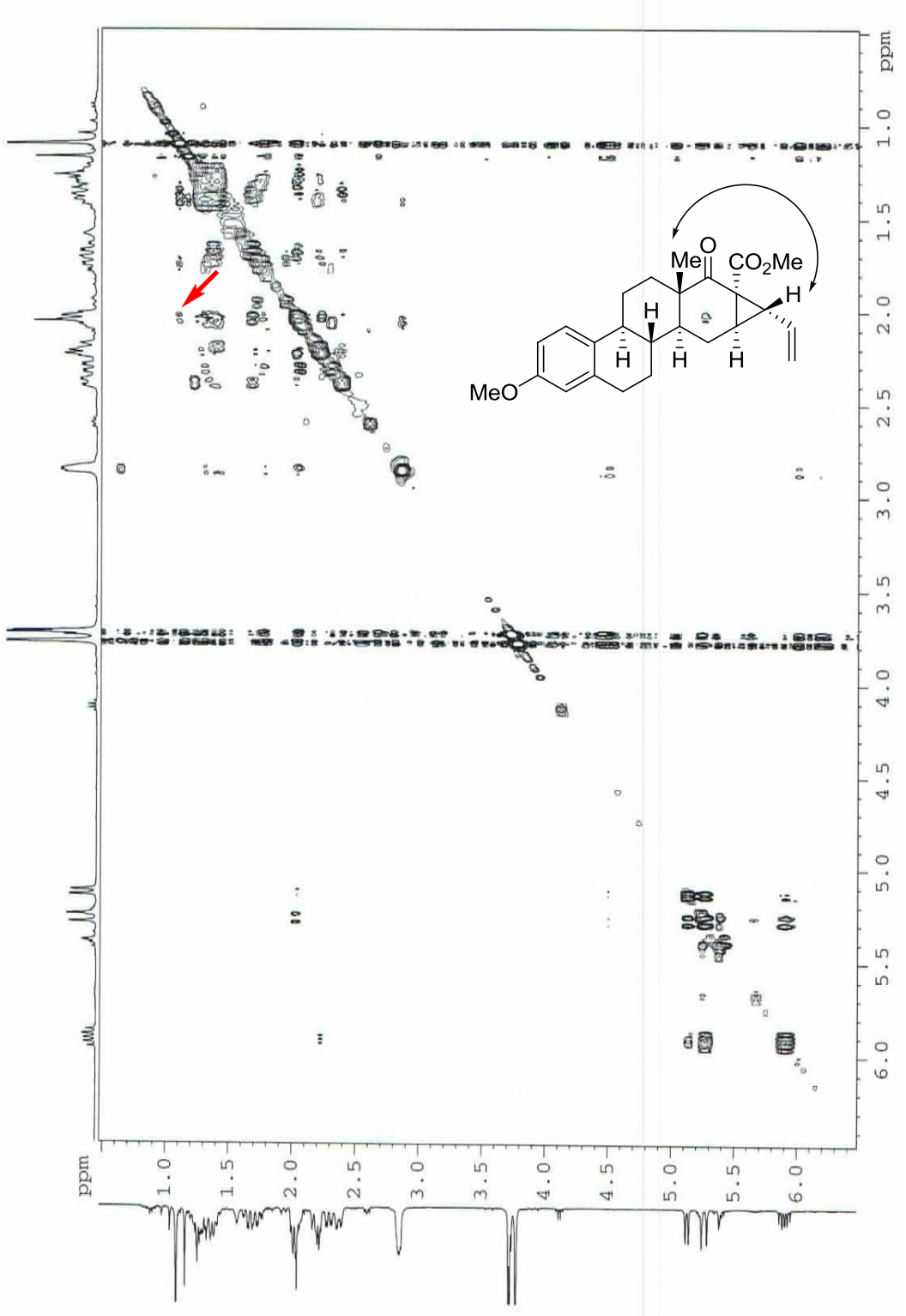
5.0
5.5
6.0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O
CO2Me
H
H
H
H
MeO
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4.0
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5.0
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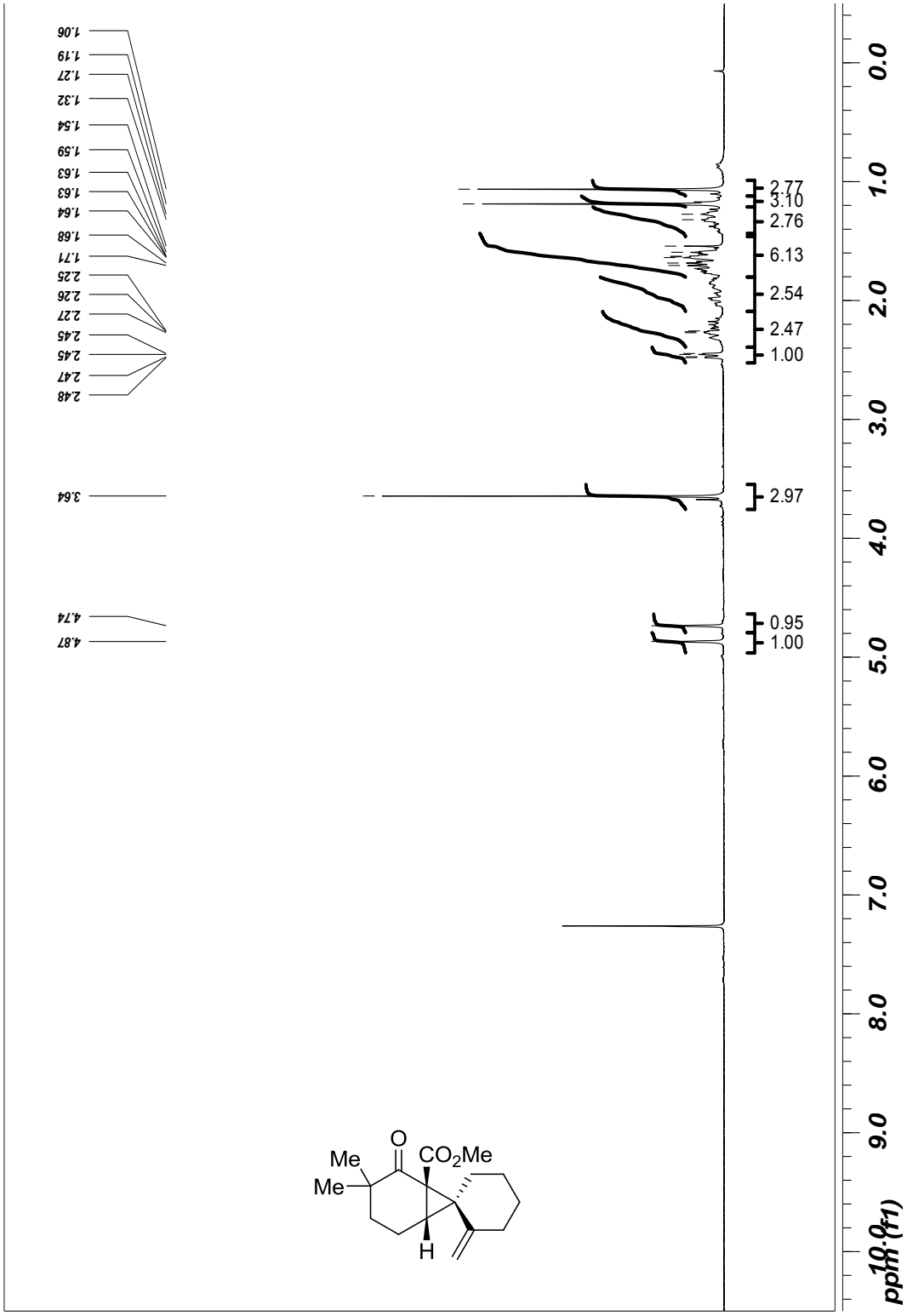
6.0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1.68
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2.26
2.27
2.45
2.45
2.47
2.48
3.64
4.74
4.87
2.77
3.10
2.76
6.13
2.54
2.47
1.00
2.97
0.95
1.00
O
Me
Me
CO2Me
H
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4.0
5.0
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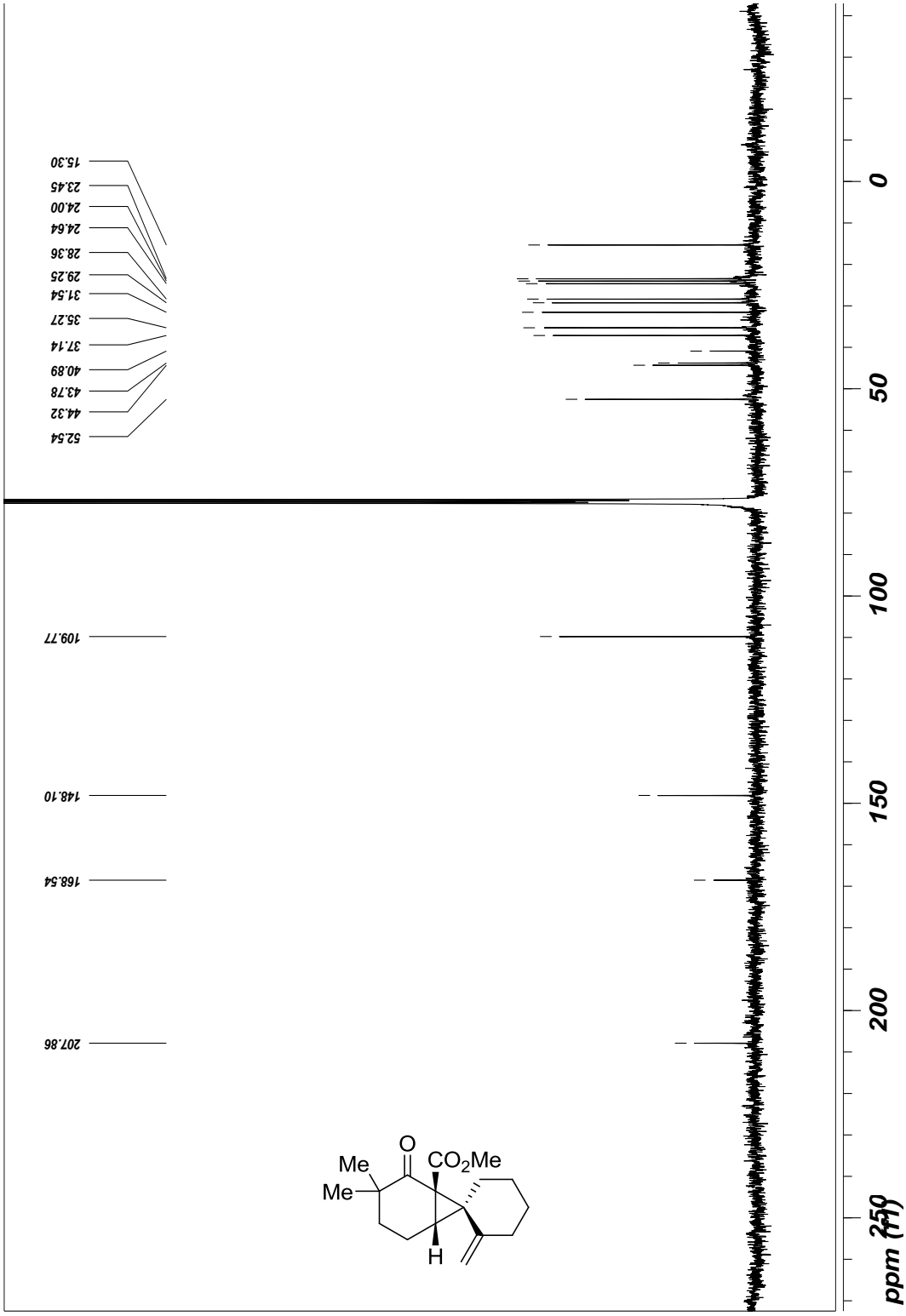
8.0
9.0
10.0
ppm (f1)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35.27
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43.78
44.32
52.54
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207.86
O
CO2Me
Me
Me
H
0
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200
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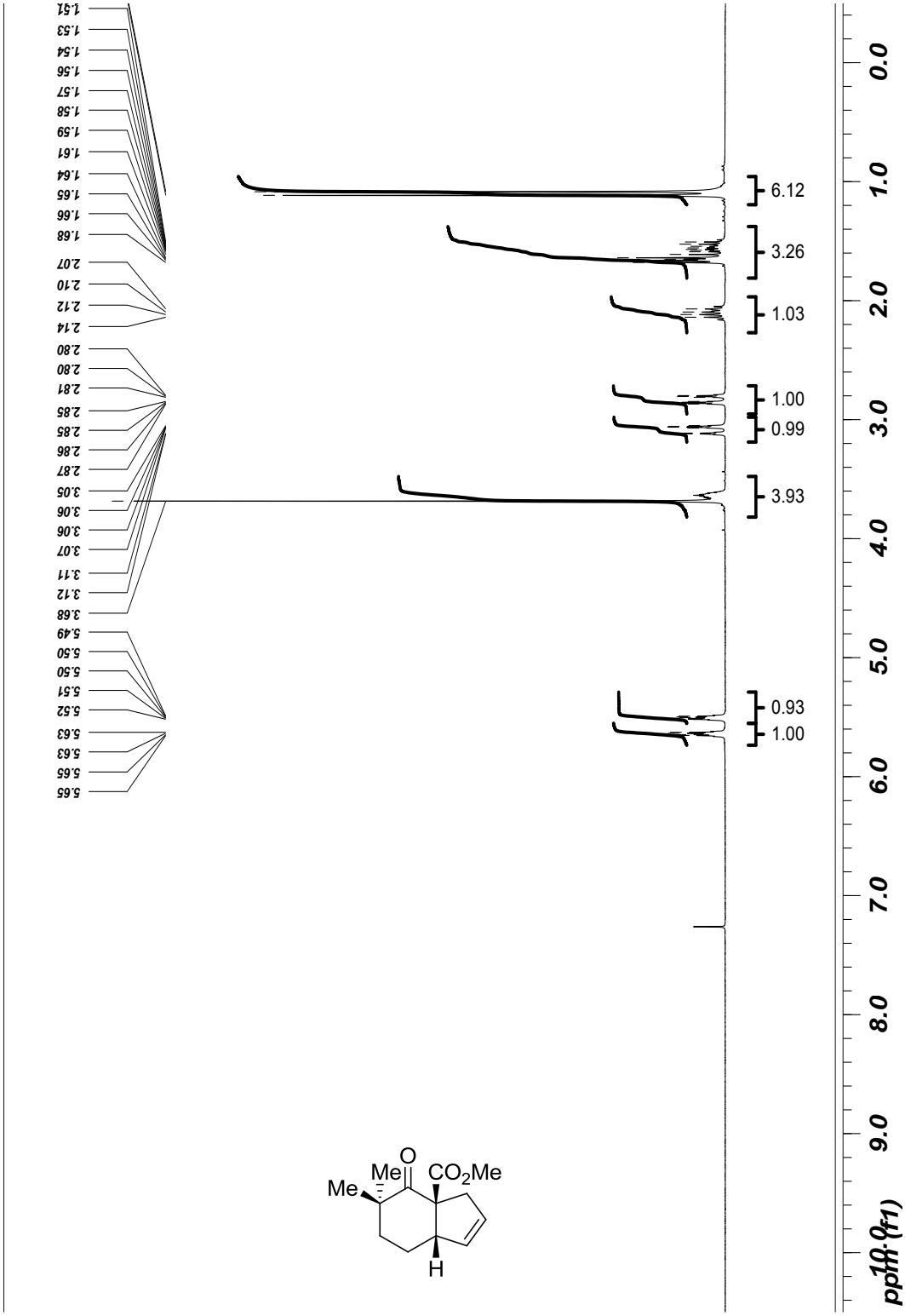
ppm (f1)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1.61
1.64
1.65
1.66
1.68
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2.10
2.12
2.14
2.80
2.80
2.81
2.85
2.85
2.86
2.87
3.05
3.06
3.06
3.07
3.11
3.12
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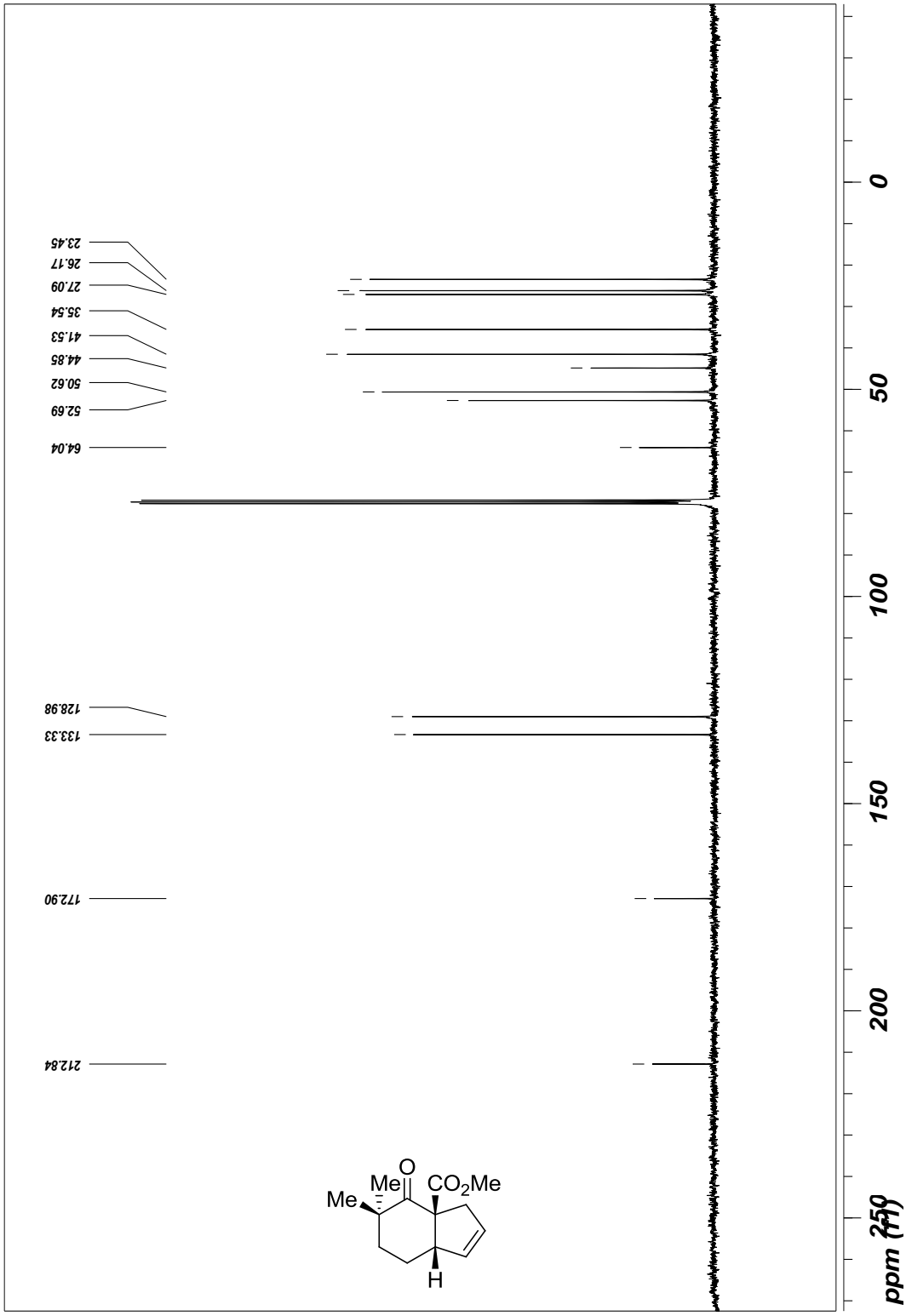
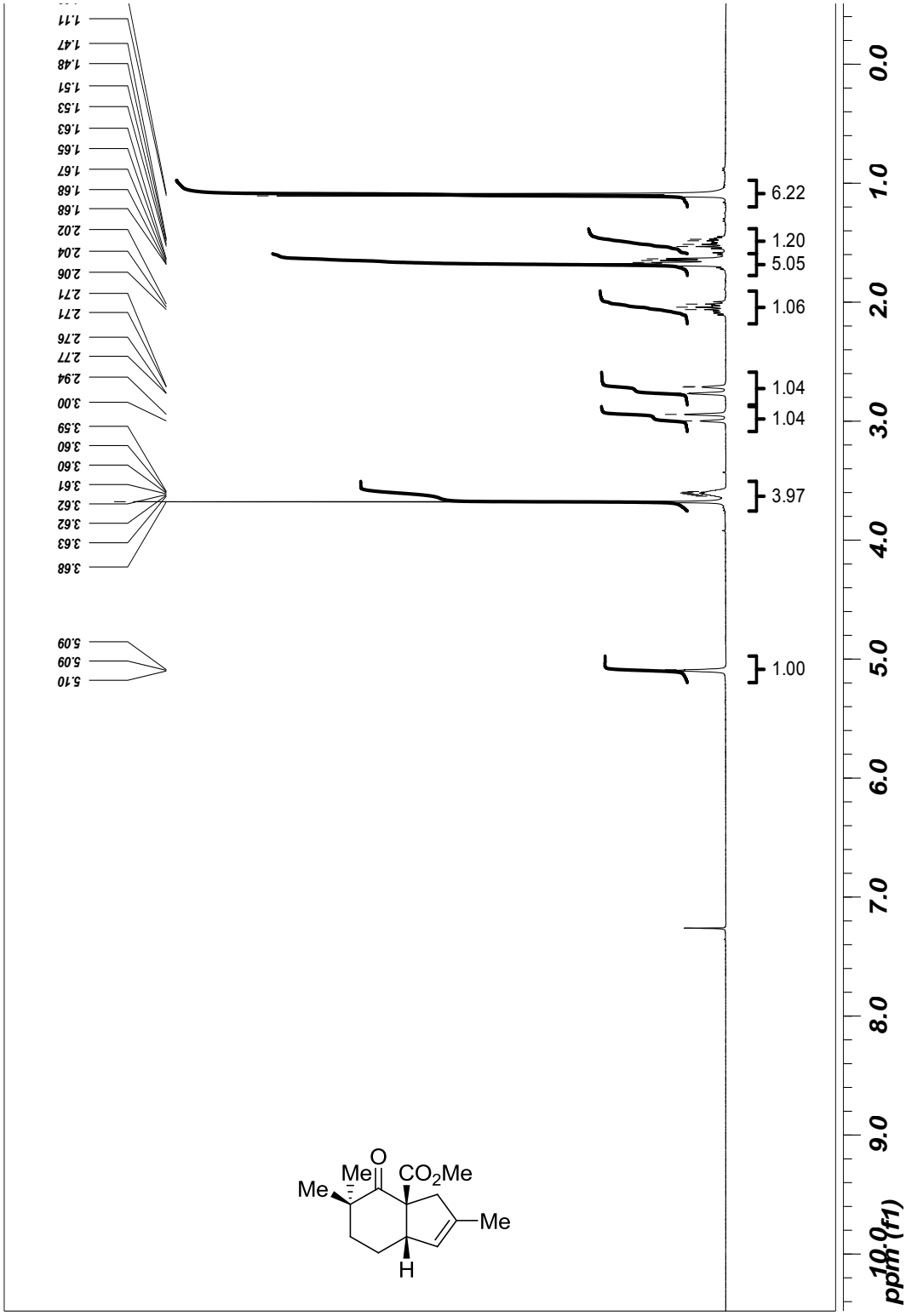
5.50
5.50
5.51
5.52
5.63
5.63
5.65
5.65
6.12
3.26
1.03
1.00
0.99
3.93
0.93
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
ppm (f1)
Me
Me
O
CO2Me
H


212.84
172.90
133.33
128.98
64.04
52.69
50.62
44.85
41.53
35.54
27.09
26.17
23.45
Me
Me
O
CO2Me
H
0
50
100
150
200
250
ppm (f1)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1.47
1.48
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1.63
1.65
1.67
1.68
1.68
2.02
2.04
2.06
2.71
2.71
2.76
2.77
2.94
3.00
3.59
3.60
3.60
3.61
3.62
3.62
3.63
3.68
5.09
5.09
5.10
6.22
1.20
5.05
1.06
1.04
1.04
3.97
1.00
0.0
1.0
2.0
3.0
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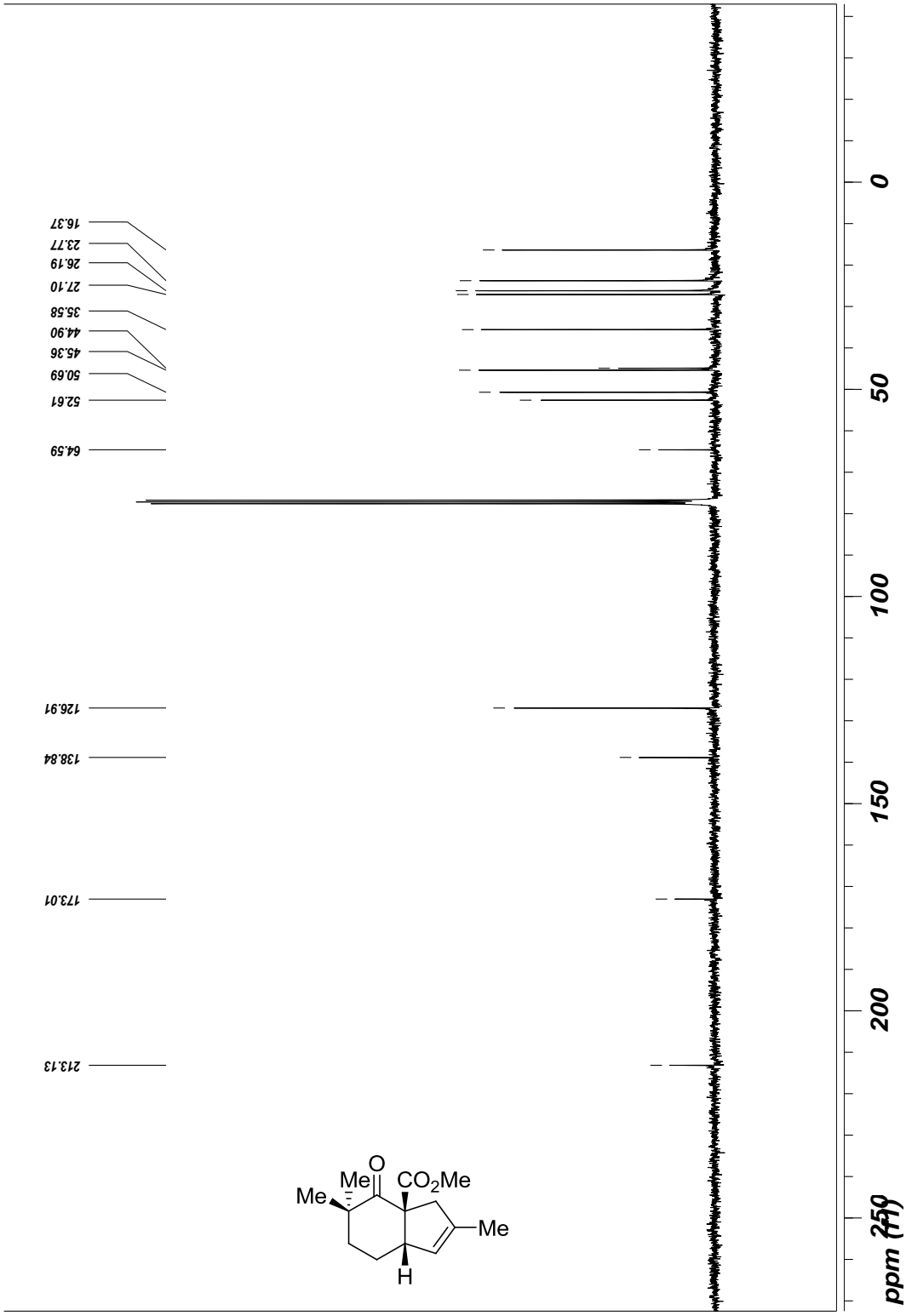
5.0
6.0
7.0
8.0
9.0
10.0
ppm (f1)
O
Me
CO2Me
Me
Me
H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23.77
26.19
27.10
35.58
44.90
45.36
50.69
52.61
64.59
126.91
138.84
173.01
213.13
O
Me
CO2Me
Me
Me
H
0
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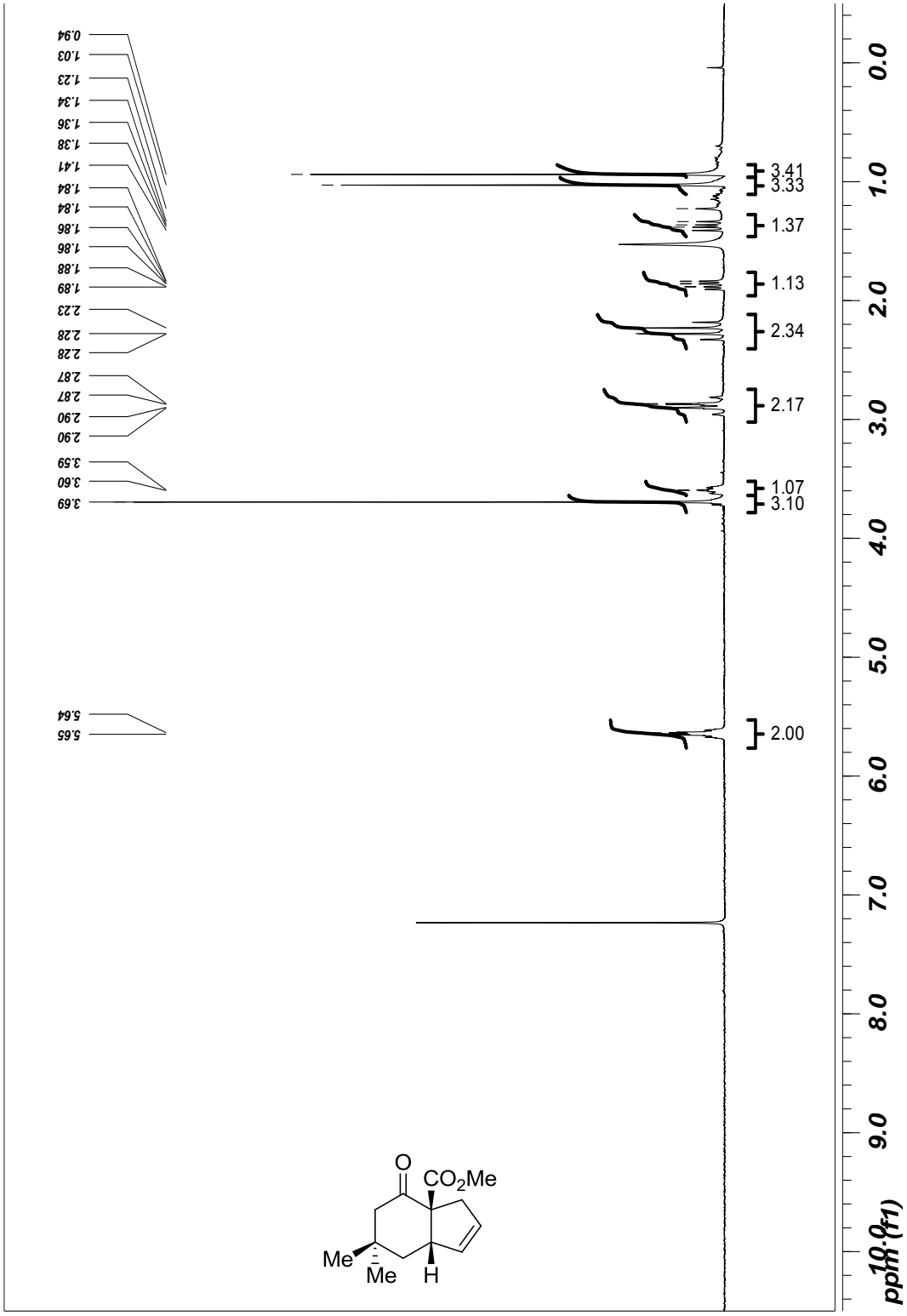
100
150
200
250
ppm (f1)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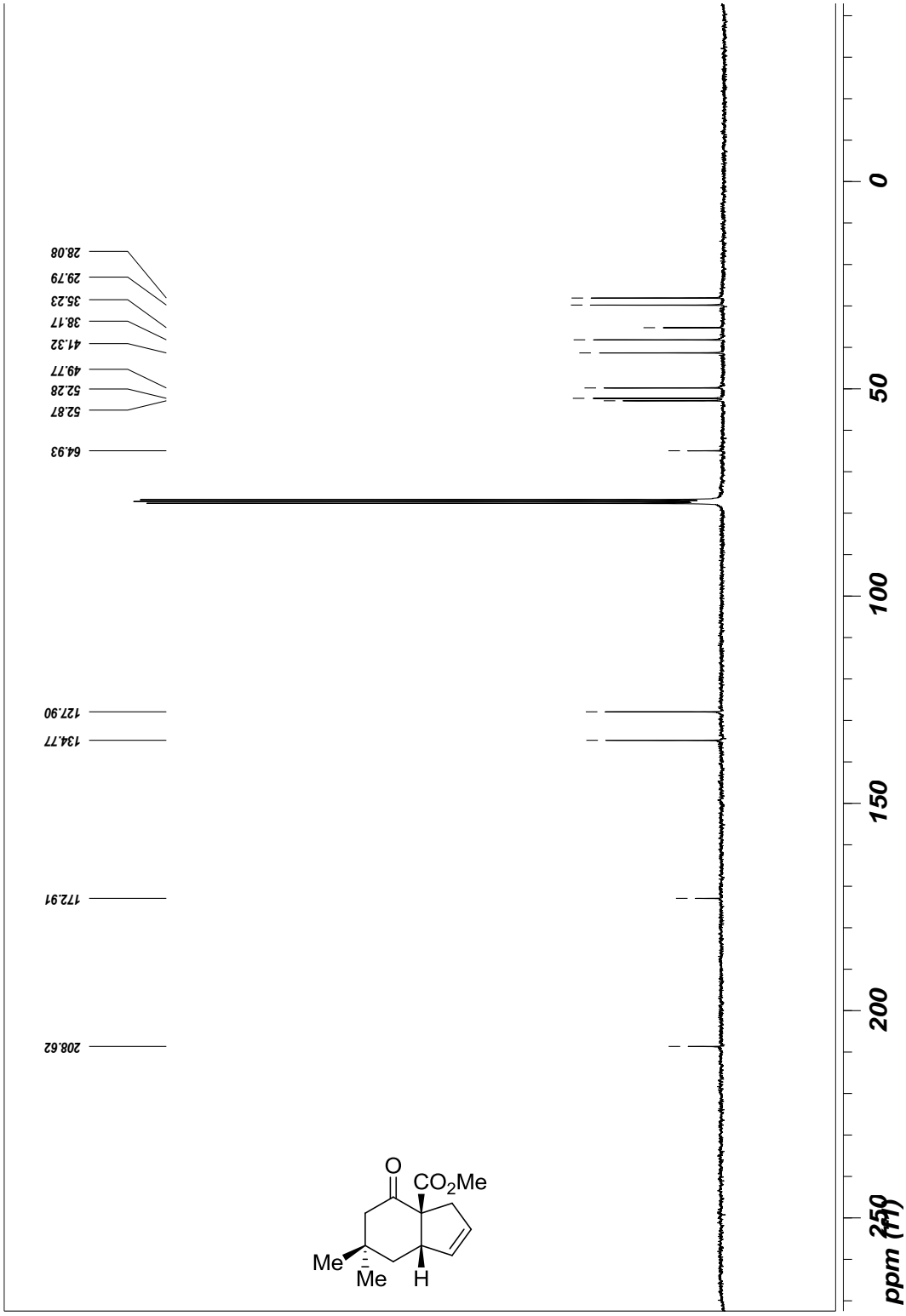
1.03
1.23
1.34
1.36
1.38
1.41
1.84
1.84
1.86
1.86
1.88
1.89
2.23
2.28
2.28
2.87
2.87
2.90
2.90
3.59
3.60
3.69
5.64
5.65
3.41
3.33
1.37
1.13
2.34
2.17
1.07
3.10
2.00
O
CO2Me
Me
Me
H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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172.91
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127.90
64.93
52.87
52.28
49.77
41.32
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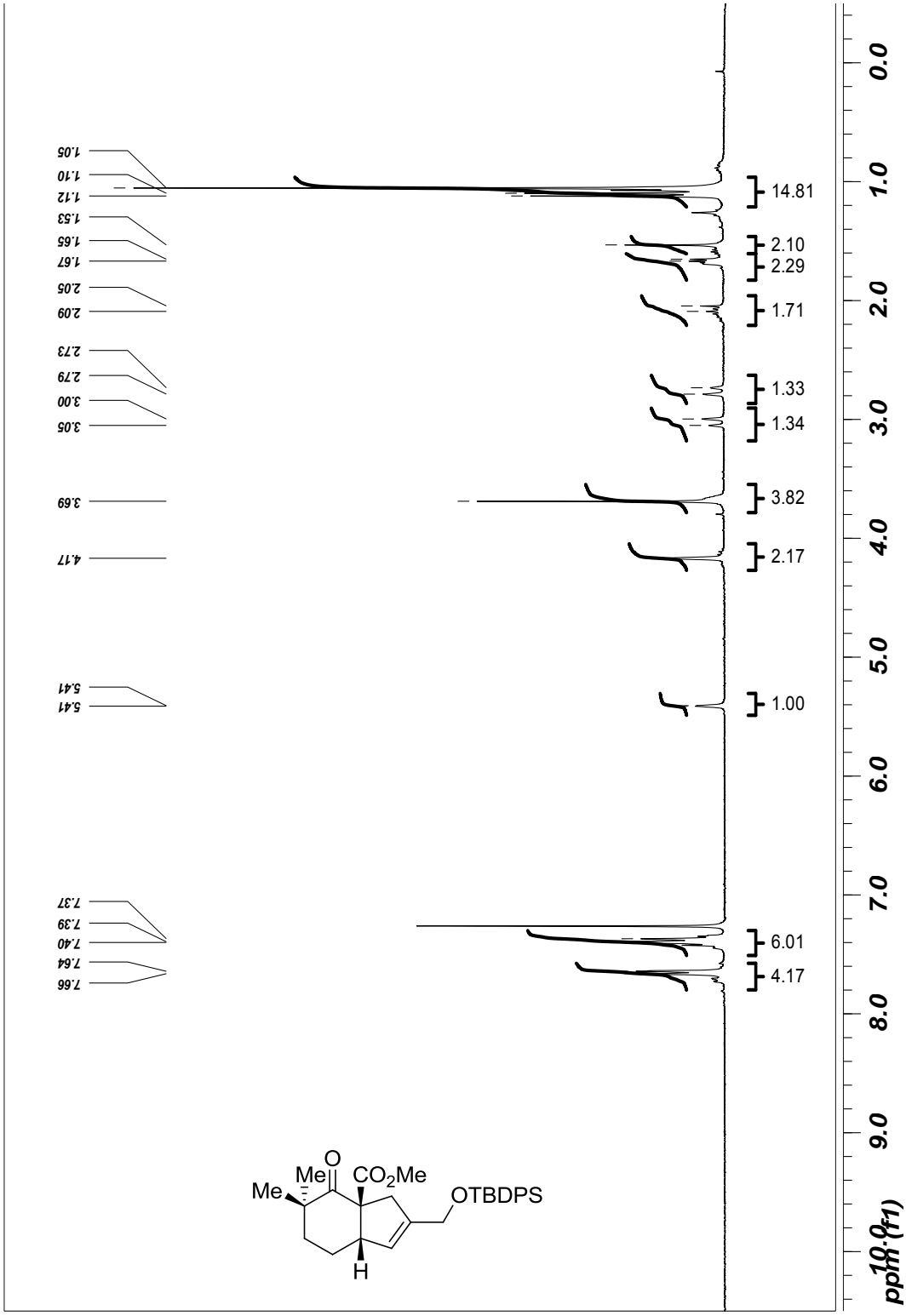
35.23
29.79
28.08
O
CO2Me
Me
Me
H
250
200
150
100
50
0
ppm (f1)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1.10
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1.53
1.65
1.67
2.05
2.09
2.73
2.79
3.00
3.05
3.69
4.17
5.41
5.41
7.37
7.39
7.40
7.64
7.66
14.81
2.10
2.29
1.71
1.33
1.34
3.82
2.17
1.00
6.01
4.17
Me
O
Me
CO2Me
OTBDPS
H
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1.0
2.0
3.0
4.0
5.0
6.0
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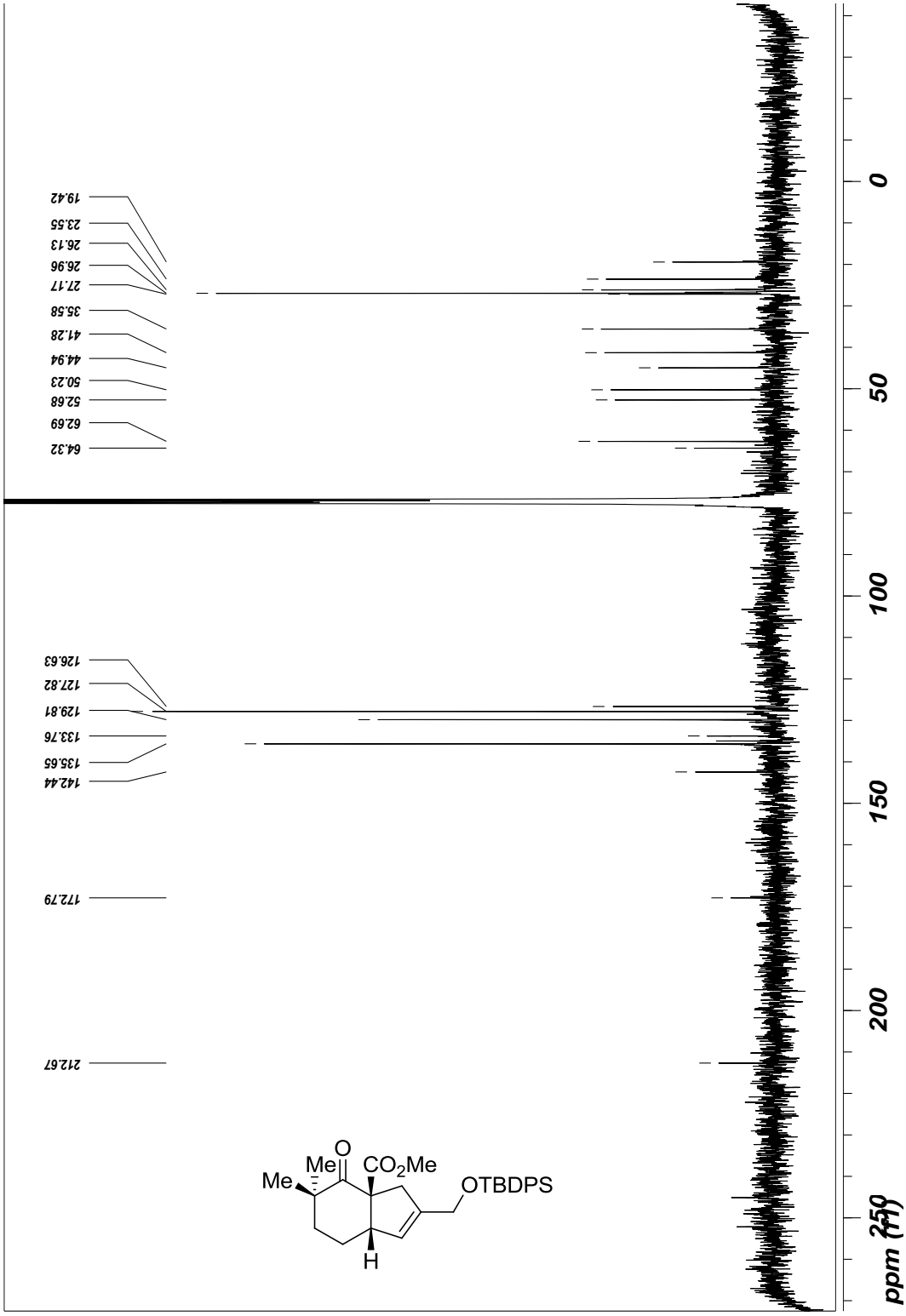
8.0
9.0
10.0
ppm (f1)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44.94
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52.68
62.69
64.32
126.63
127.82
129.81
133.76
135.65
142.44
172.79
212.67
Me
O
Me
CO2Me
OTBDPS
H
0
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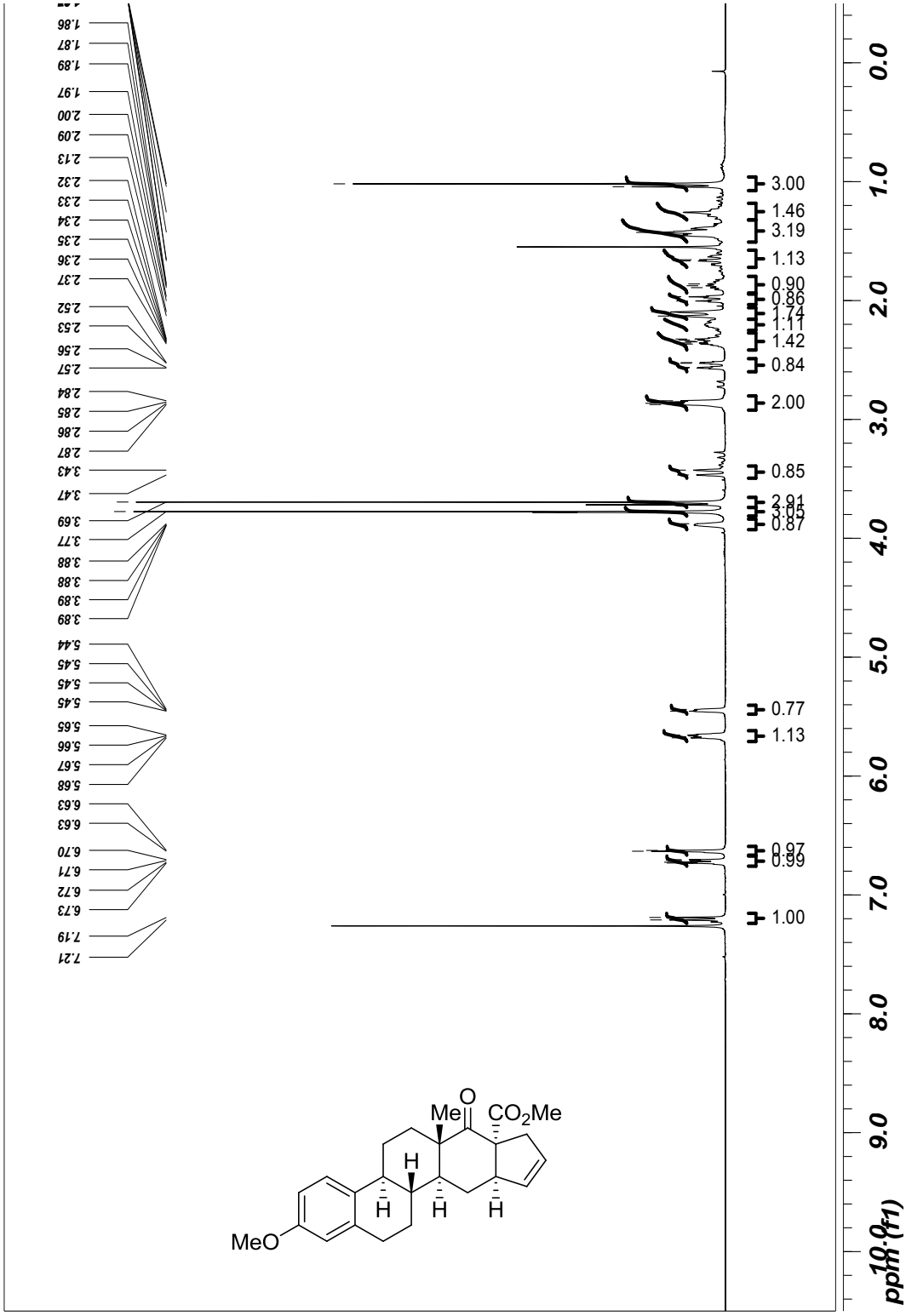
100
150
200
250
ppm (f1)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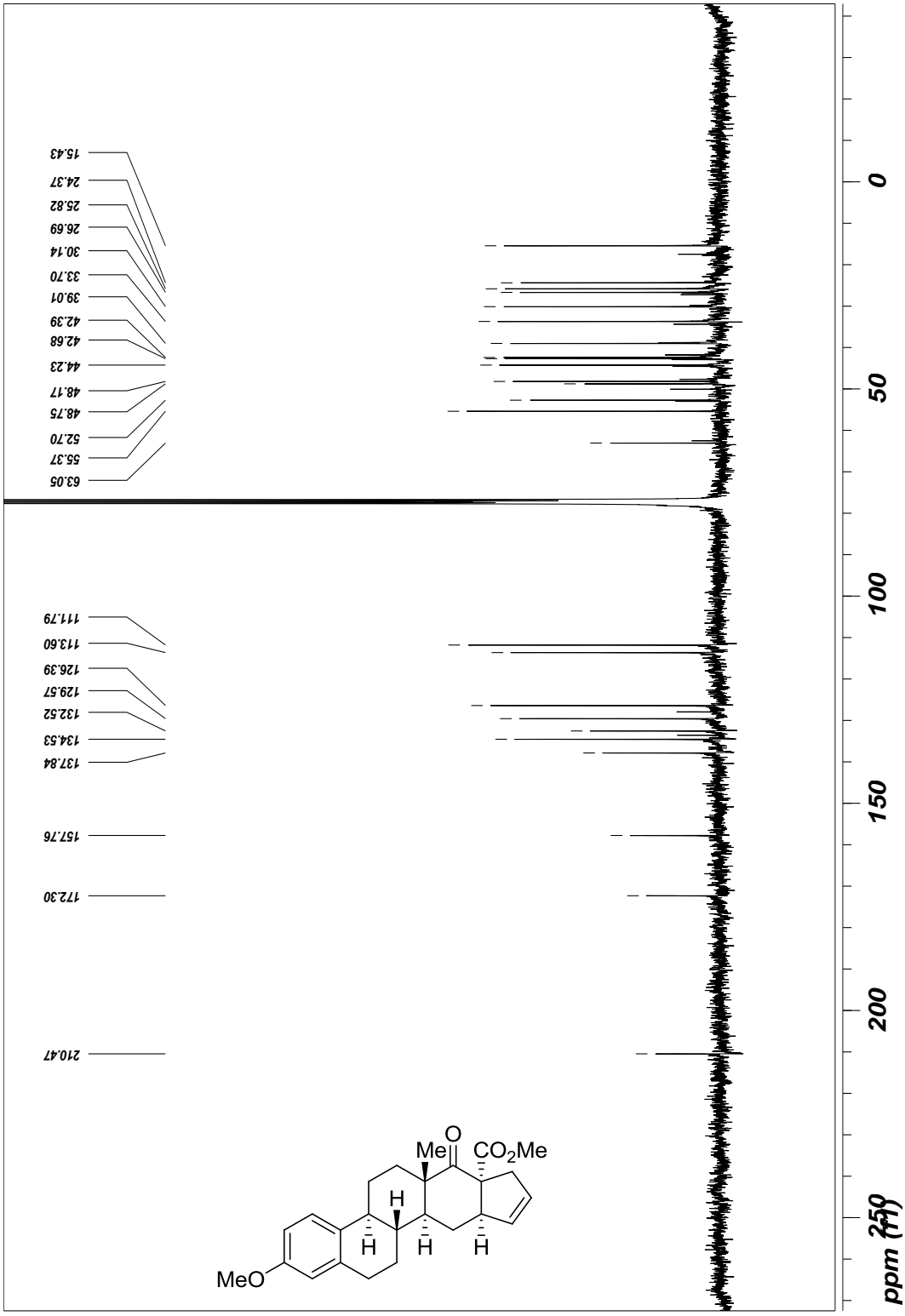
3.19
1.13
0.90
0.86
1.74
1.11
1.42
0.84
2.00
0.85
2.91
3.05
0.87
0.77
1.13
0.97
0.99
1.00
Me
O
CO2Me
H
H
H
H
MeO
ppm (f1)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0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33.70
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44.23
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48.75
52.70
55.37
63.05
111.79
113.60
126.39
129.57
132.52
134.53
137.84
157.76
172.30
210.47
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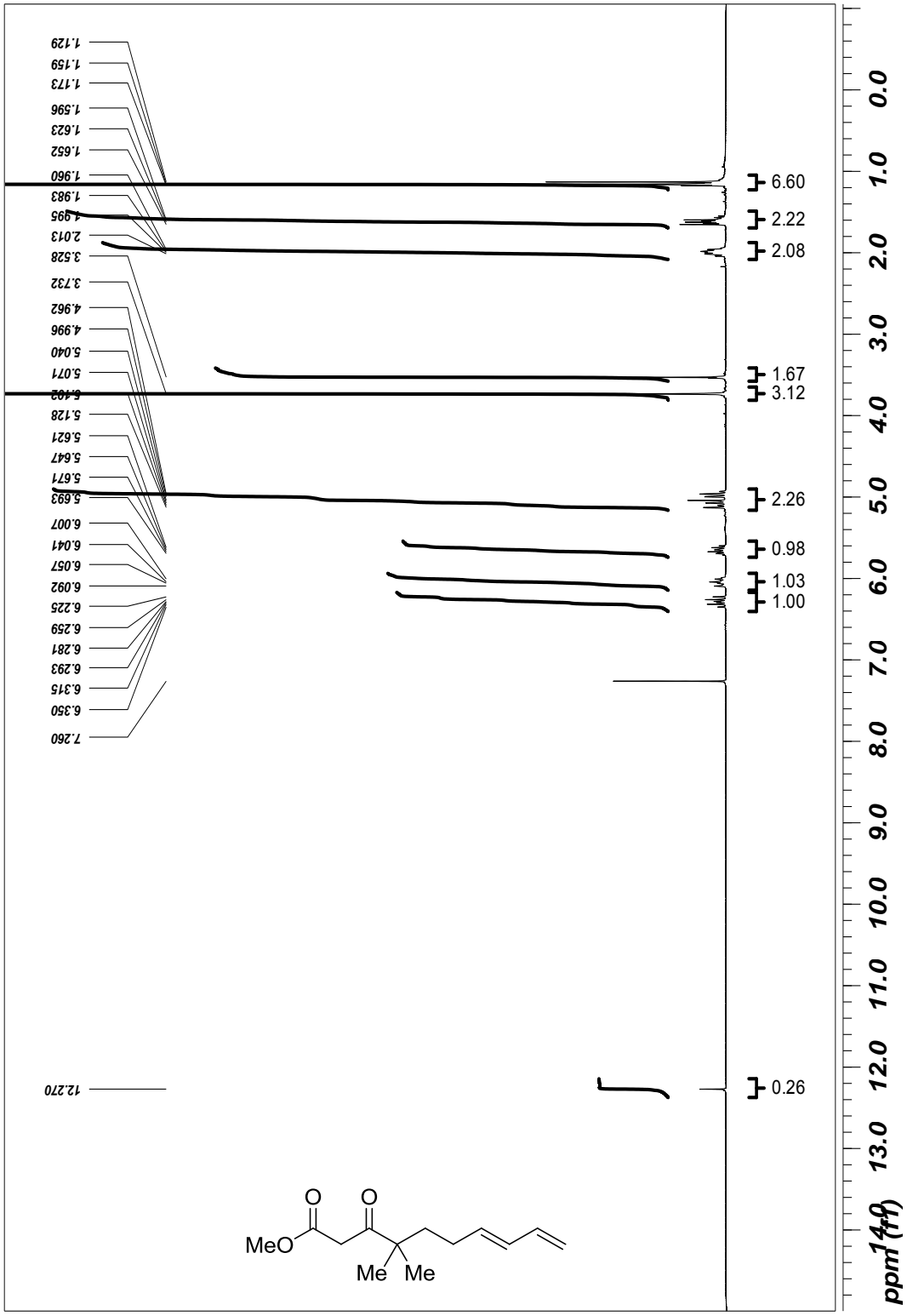
50
100
150
200
250
ppm (f1)
Me
O
CO2Me
H
H
H
H
MeO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2.013
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3.732
4.962
4.996
5.040
5.071
5.102
5.128
5.621
5.647
5.671
5.693
6.007
6.041
6.057
6.092
6.225
6.259
6.281
6.293
6.315
6.350
7.260
12.270
6.60
2.22
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2.26
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1.00
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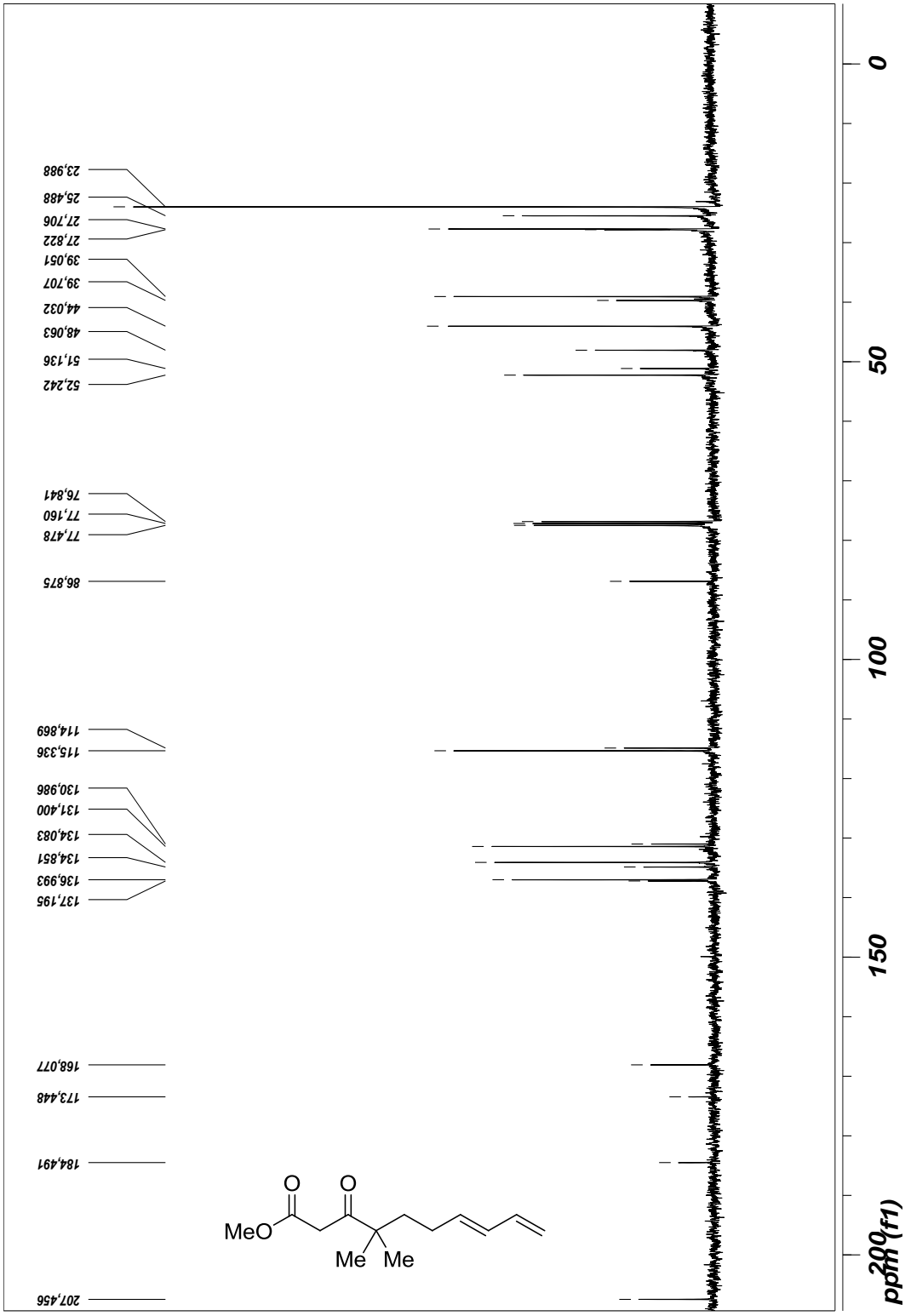
MeO
O
O
Me
Me
ppm (f1)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52,242
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77,478
86,875
114,869
115,336
130,986
131,400
134,083
134,851
136,993
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184,491
207,456
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Me
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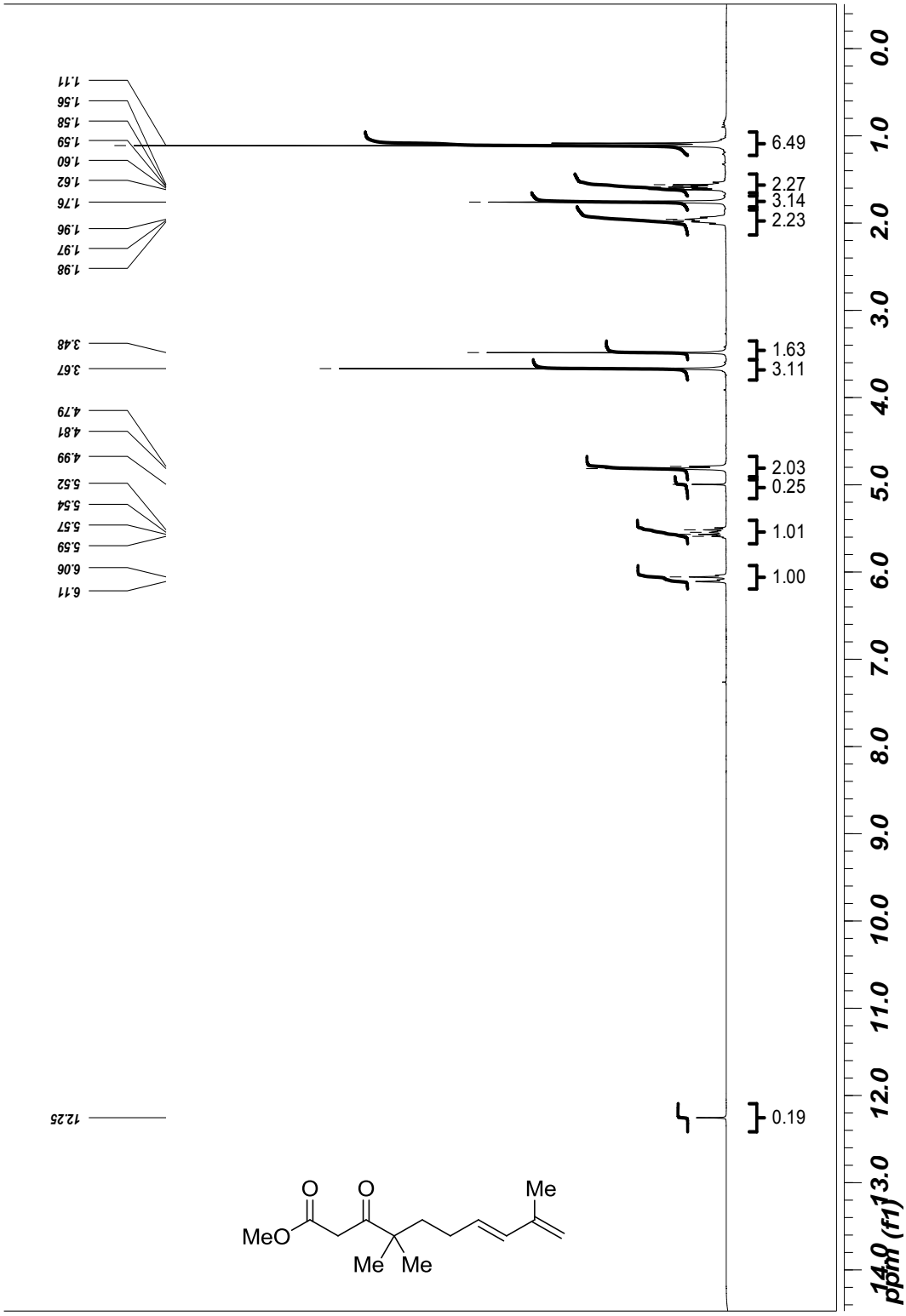
150
200
ppm (f1)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1.97
1.98
3.48
3.67
4.79
4.81
4.99
5.52
5.54
5.57
5.59
6.06
6.11
12.25
6.49
2.27
3.14
2.23
1.63
3.11
2.03
0.25
1.01
1.00
0.19
O
O
Me
MeO
Me
Me
0.0
1.0
2.0
3.0
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7.0
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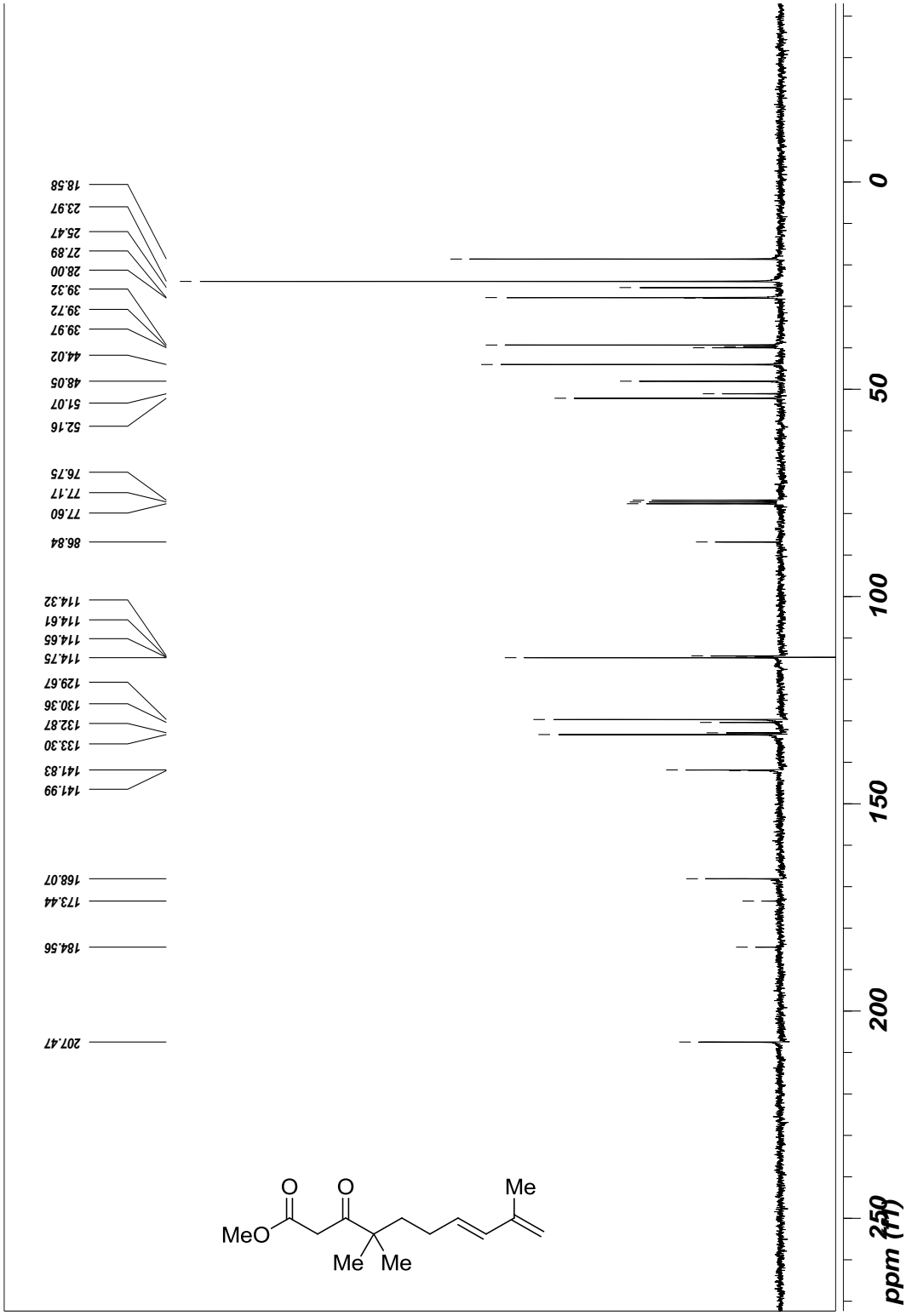
12.0
13.0
14.0
ppm (f1)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39.97
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48.05
51.07
52.16
76.75
77.17
77.60
86.84
114.32
114.61
114.65
114.75
129.67
130.36
132.87
133.30
141.83
141.99
168.07
173.44
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207.47
O
O
Me
MeO
Me
Me
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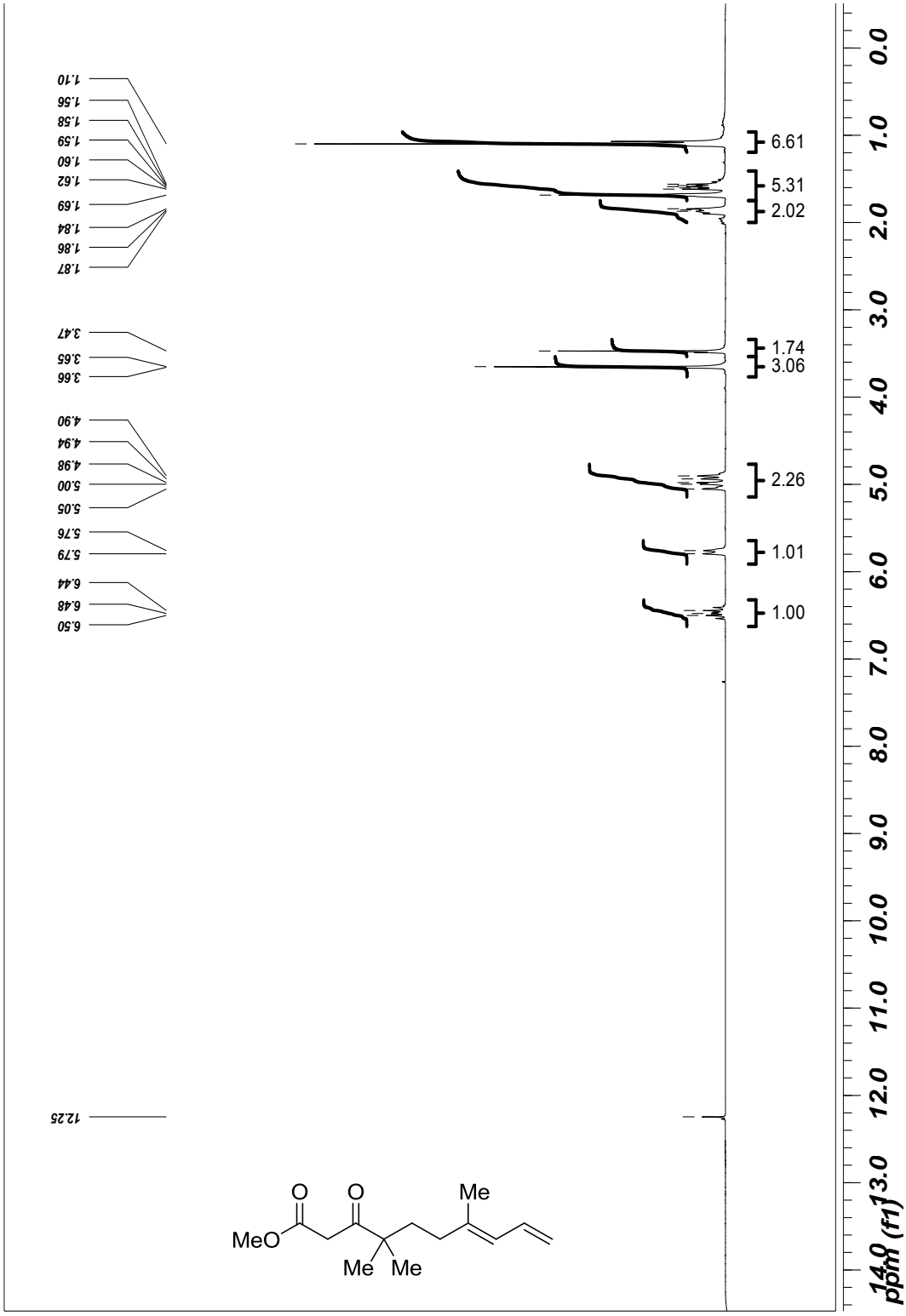
150
200
250
ppm (f1)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6.44
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5.76
5.05
5.00
4.98
4.94
4.90
3.66
3.65
3.47
1.87
1.86
1.84
1.69
1.62
1.60
1.59
1.58
1.56
1.10
6.61
5.31
2.02
1.74
3.06
2.26
1.01
1.00
MeO
O
O
Me
Me
Me
13.0
12.0
11.0
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6.0
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2.0
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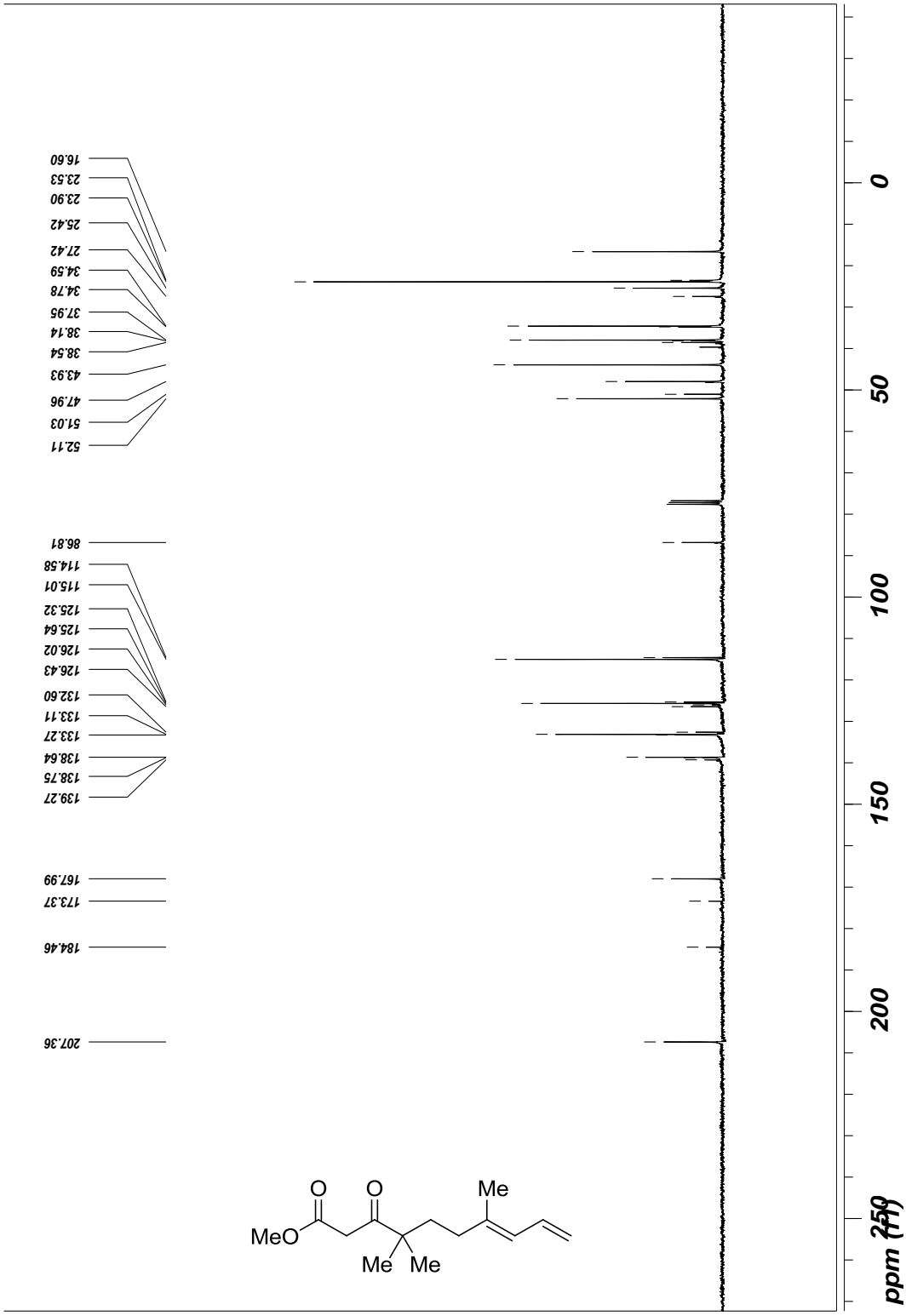
0.0
ppm (f1)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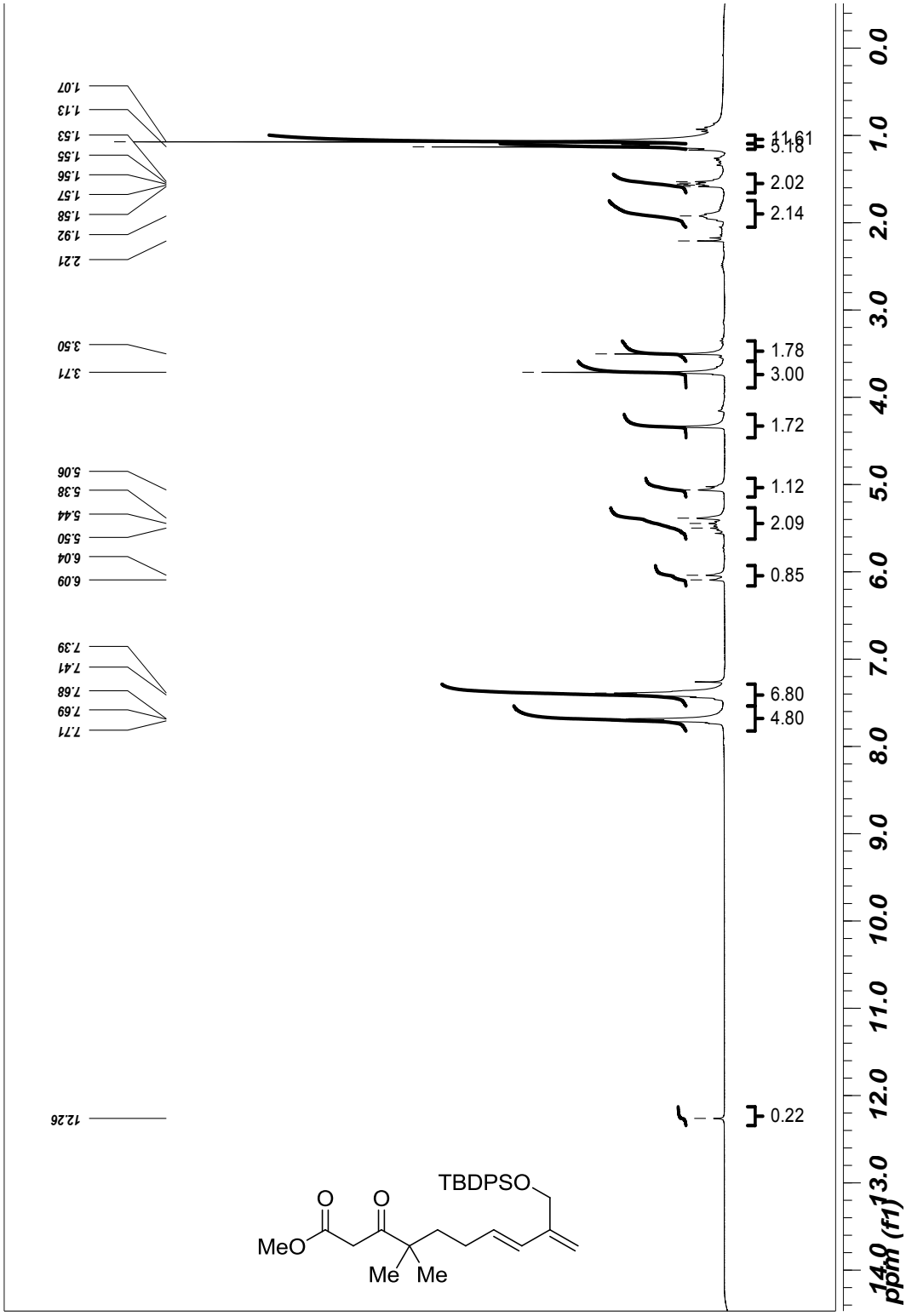
37.95
38.14
38.54
43.93
47.96
51.03
52.11
86.81
114.58
115.01
125.32
125.64
126.02
126.43
132.60
133.11
133.27
138.64
138.75
139.27
167.99
173.37
184.46
207.36
O
O
Me
MeO
Me
Me
0
50
100
150
200
250
ppm (f1)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5.38
5.44
5.50
6.04
6.09
7.39
7.41
7.68
7.69
7.71
12.26
11.61
5.18
2.02
2.14
1.78
3.00
1.72
1.12
2.09
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6.80
4.80
0.22
TBDPSO
O
O
MeO
Me
Me
0.0
1.0
2.0
3.0
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12.0
13.0
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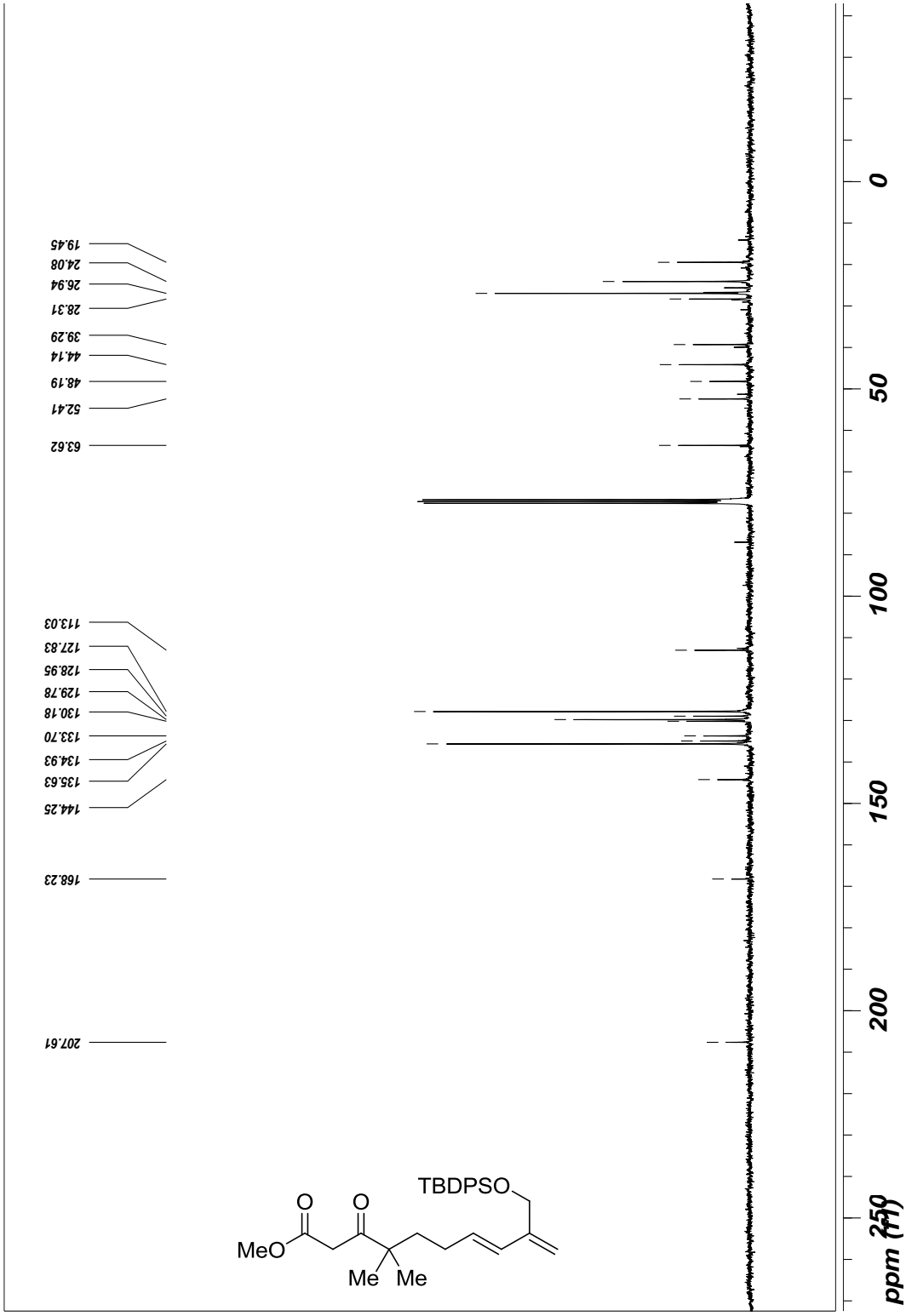
ppm (f1)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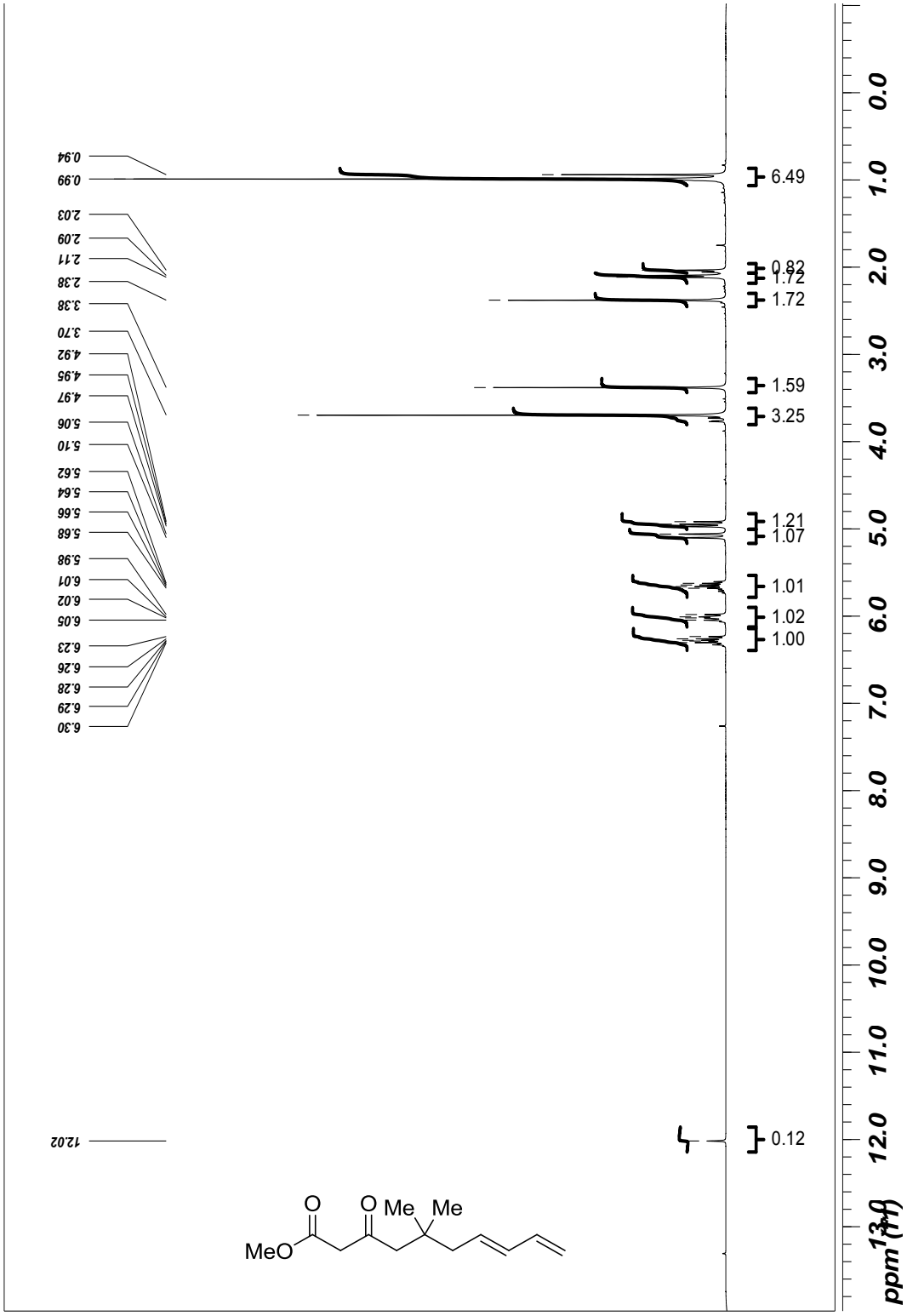
135.63
134.93
133.70
130.18
129.78
128.95
127.83
113.03
63.62
52.41
48.19
44.14
39.29
28.31
26.94
24.08
19.45
0
50
100
150
200
250
ppm (f1)
TBDPSO
O
O
MeO
Me
Me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2.11
2.38
3.38
3.70
4.92
4.95
4.97
5.06
5.10
5.62
5.64
5.66
5.68
5.98
6.01
6.02
6.05
6.23
6.26
6.28
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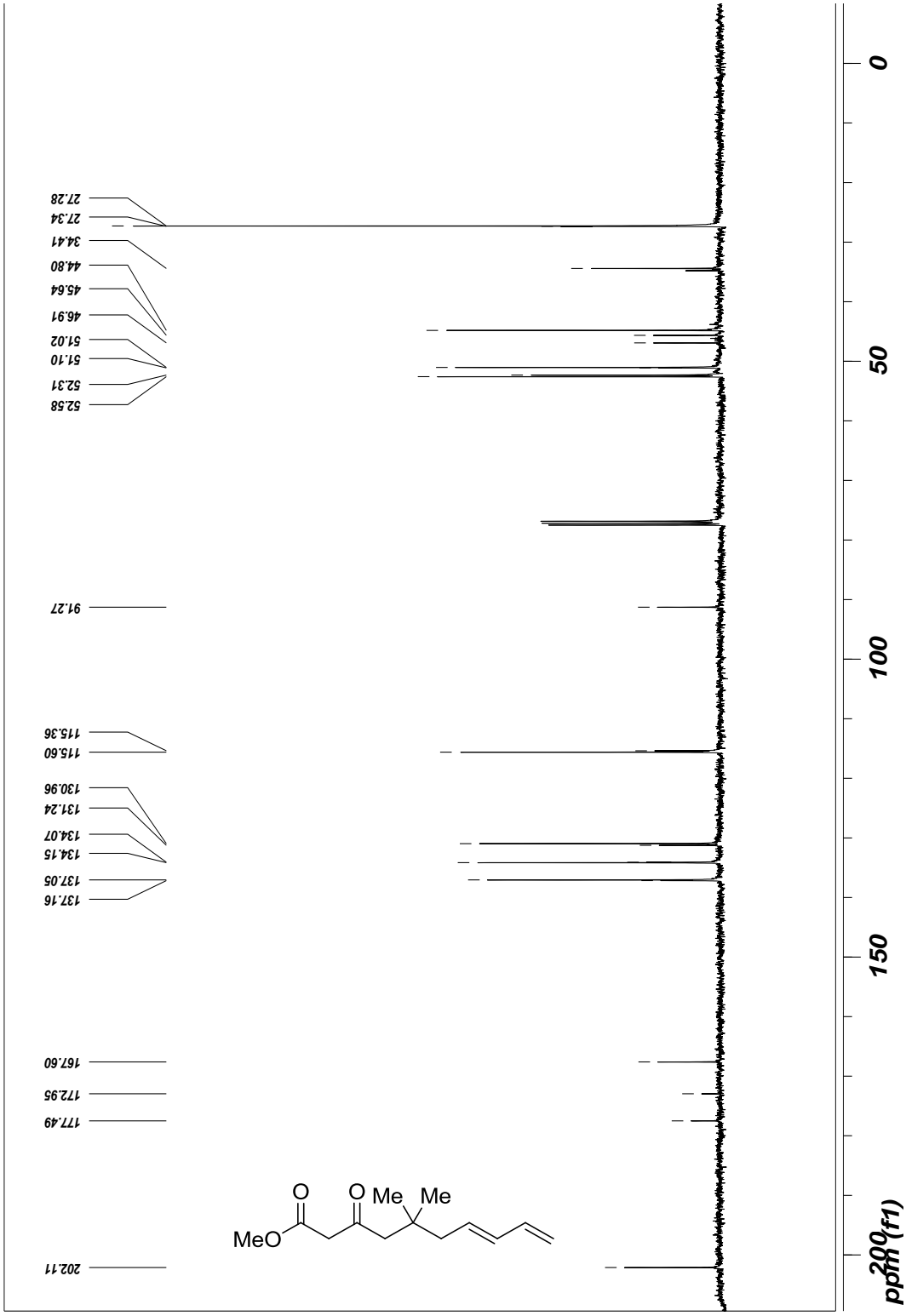
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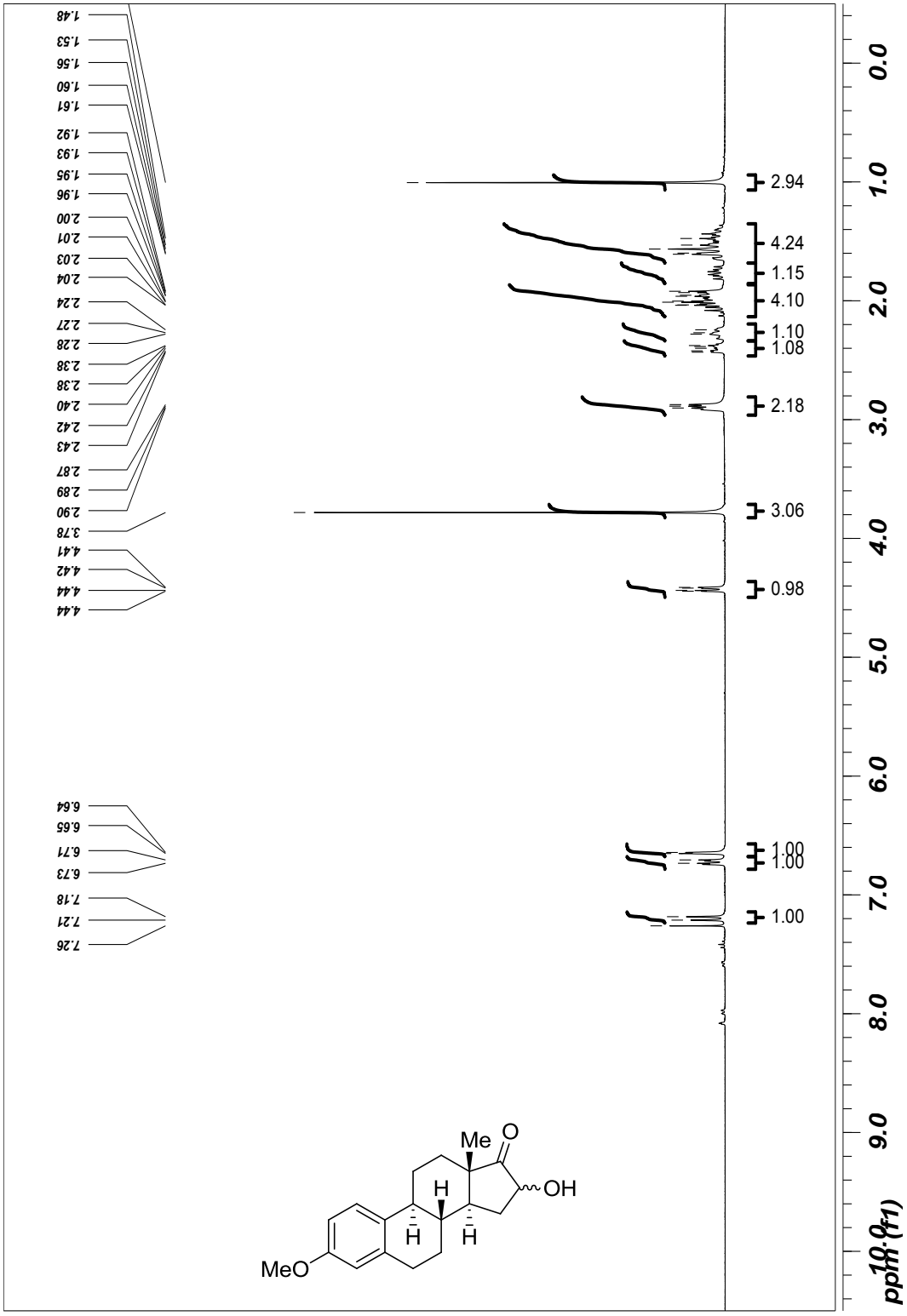
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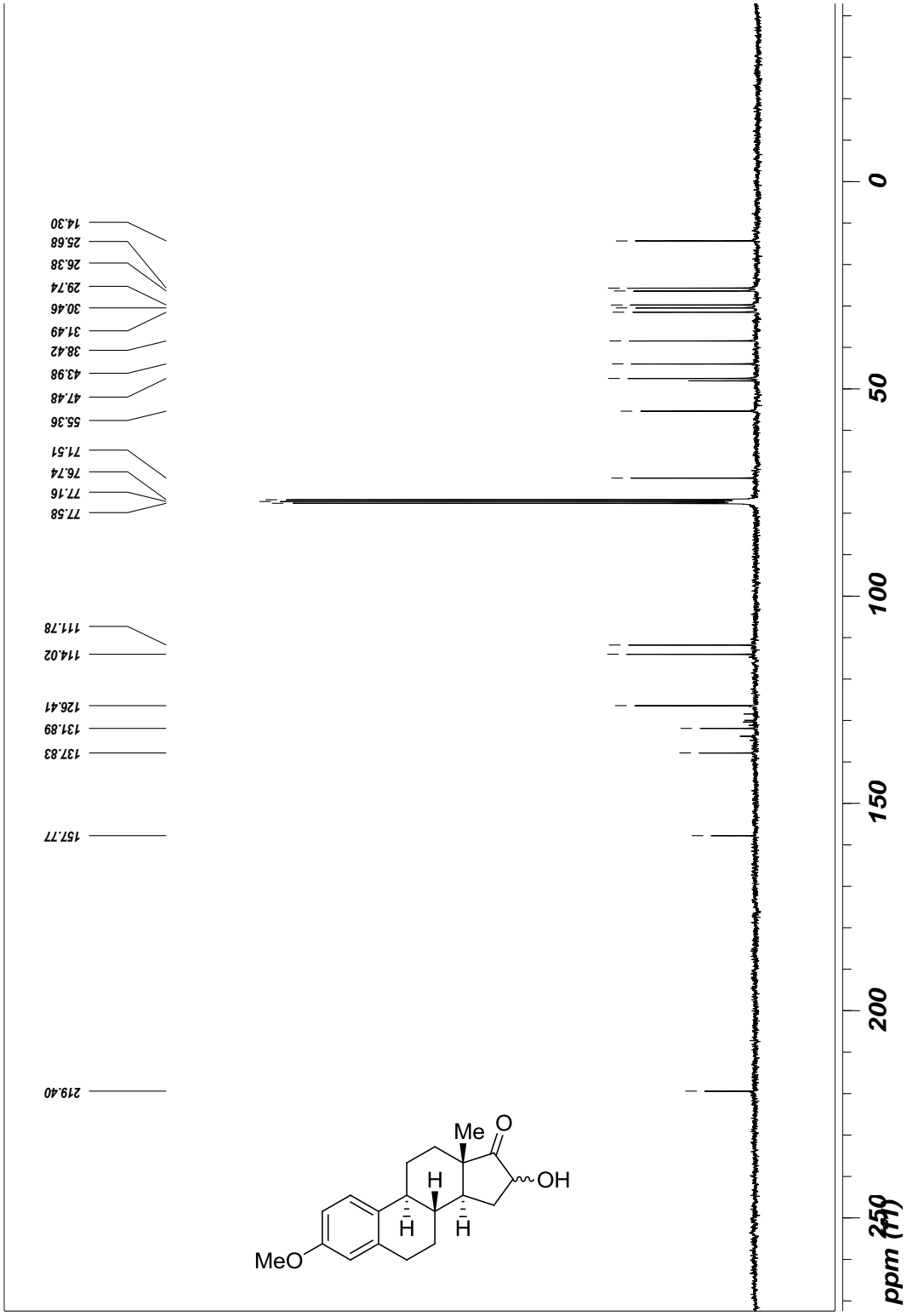
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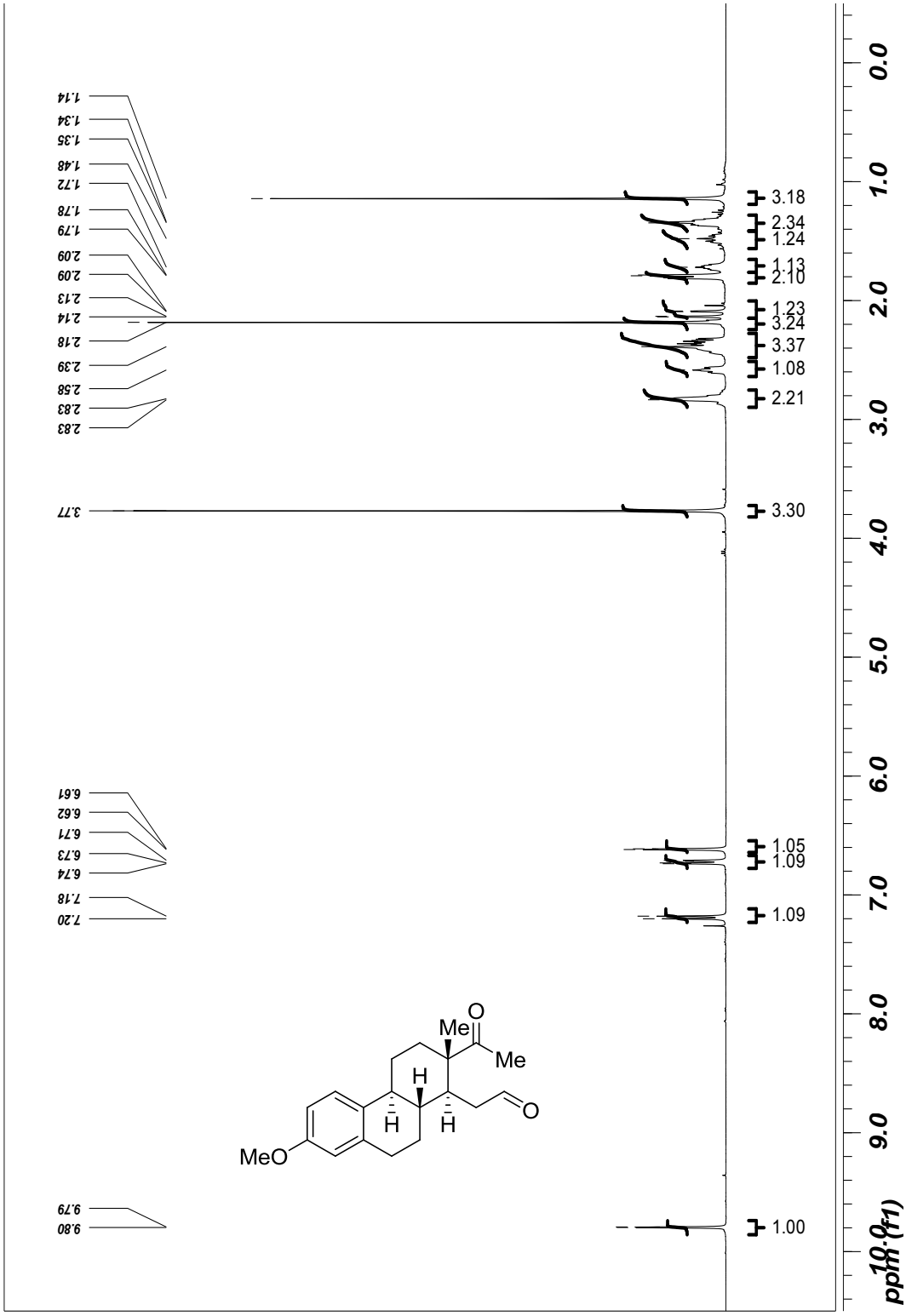
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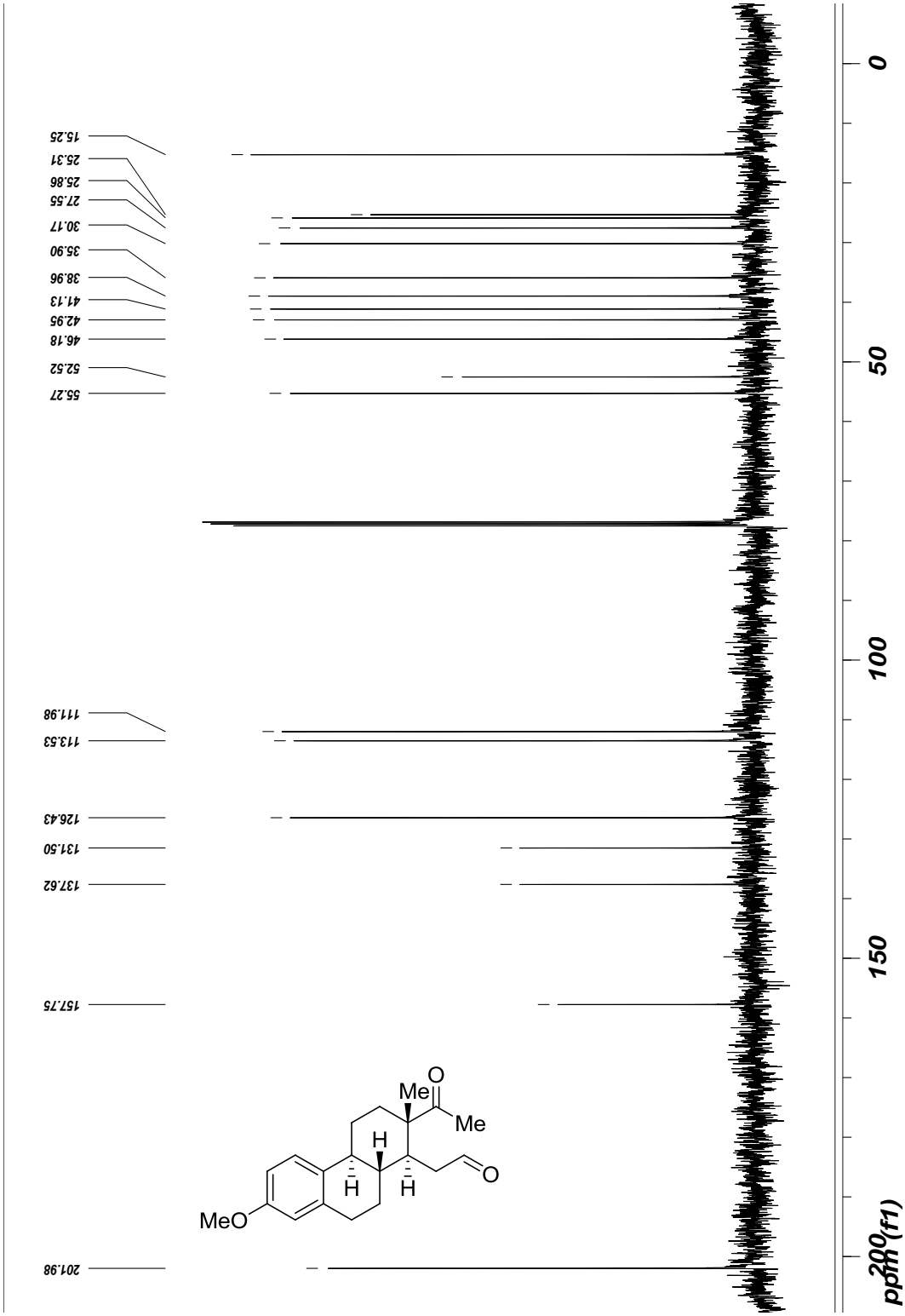
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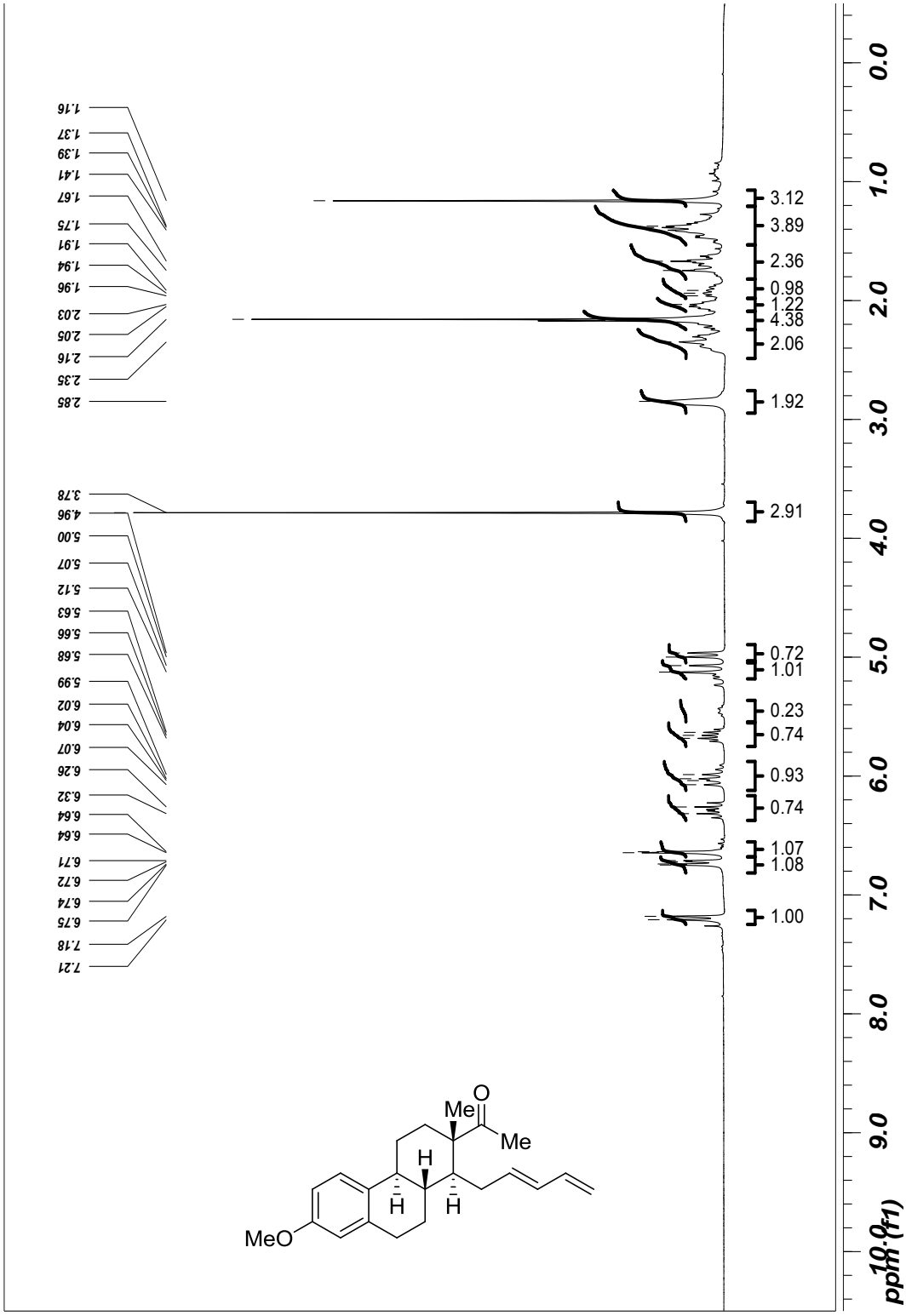
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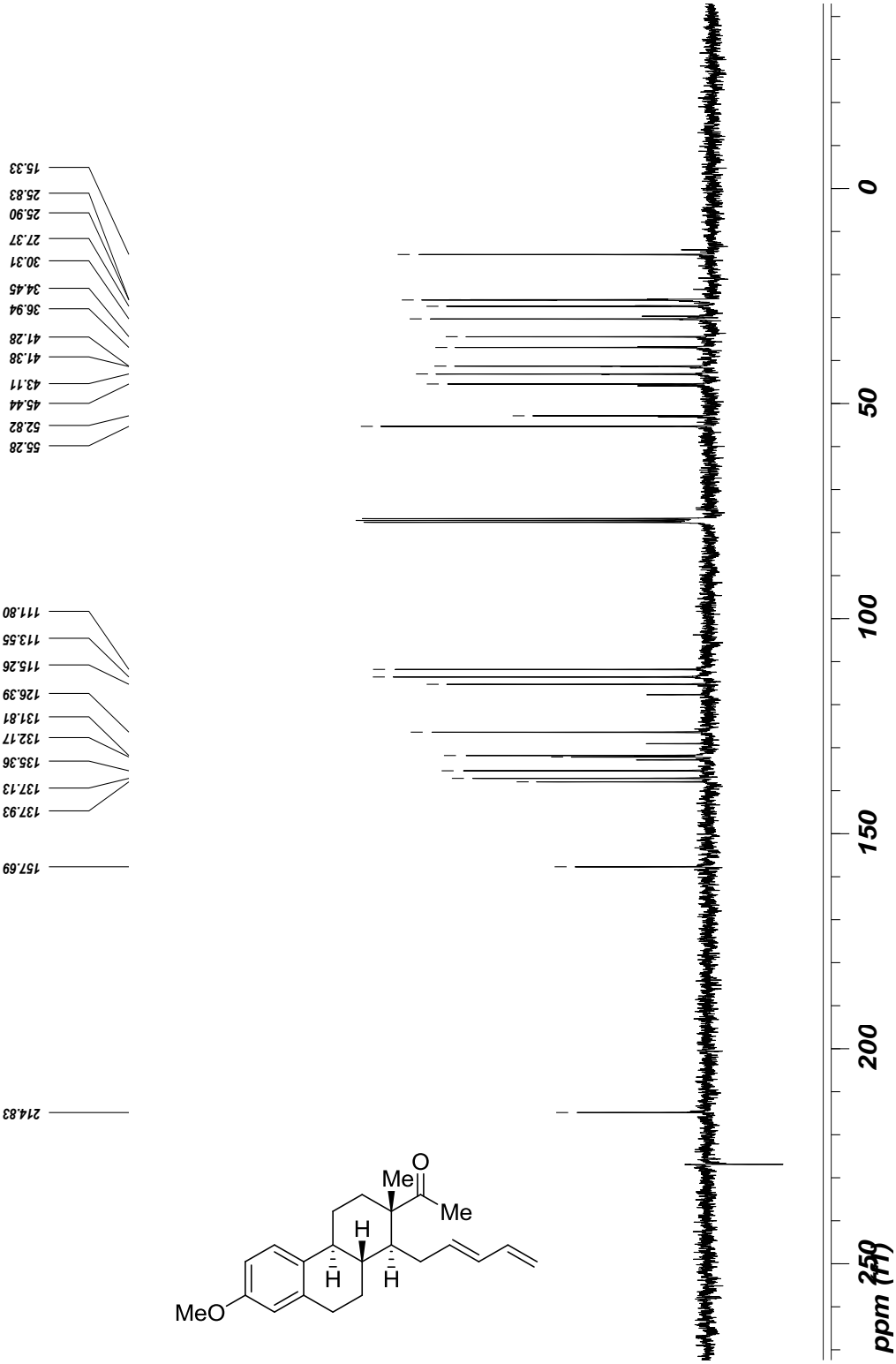
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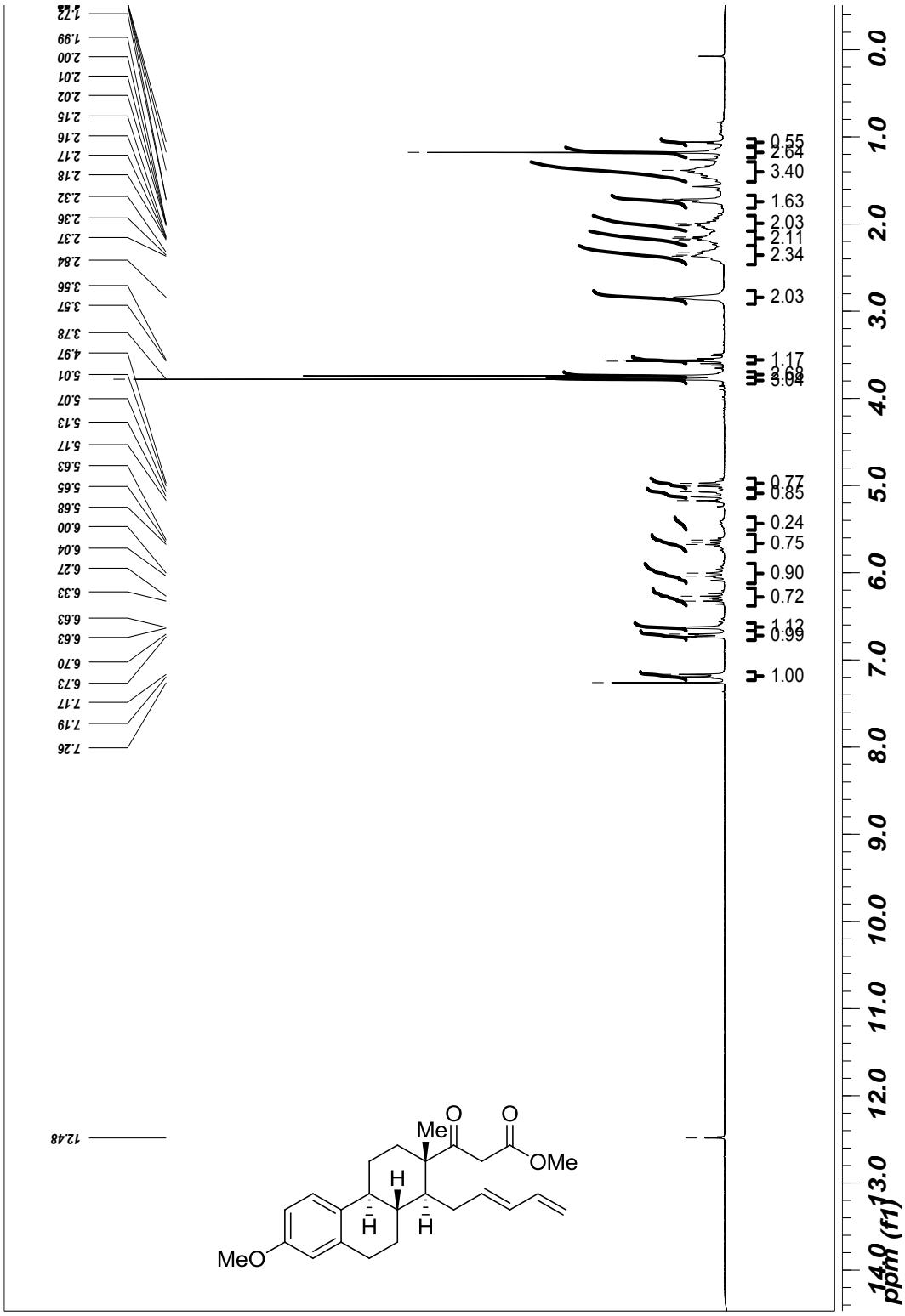
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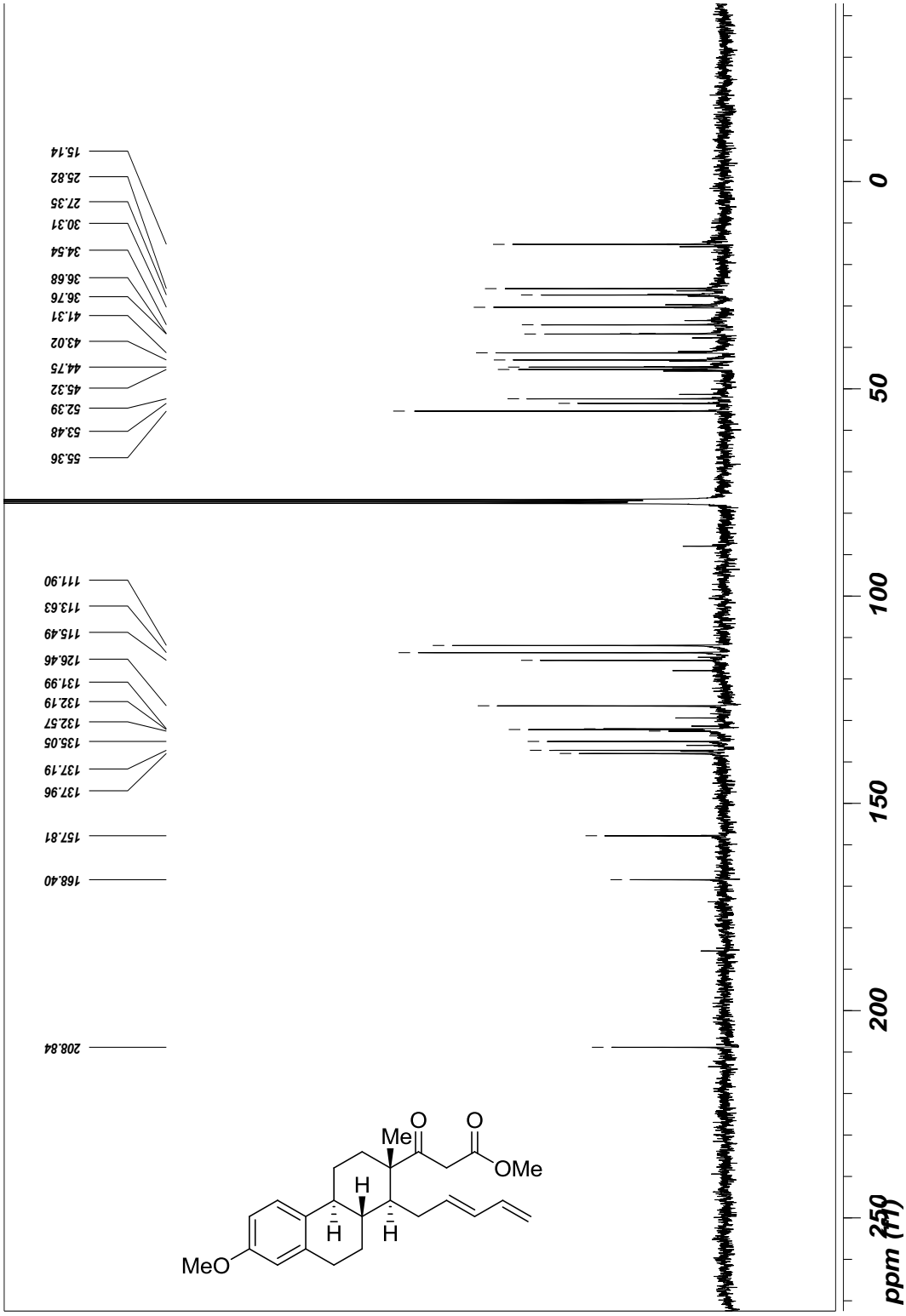
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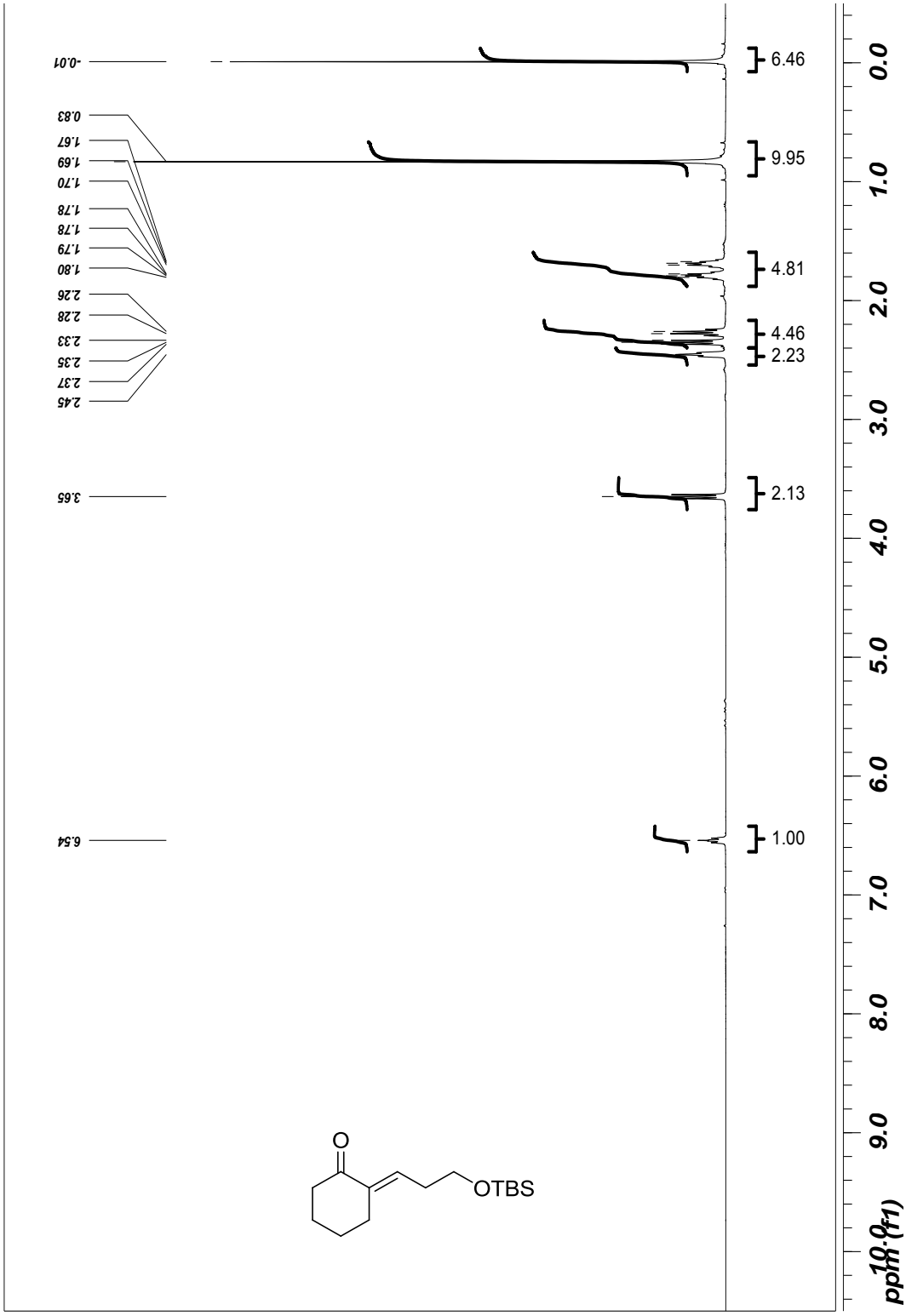
H
H
H
MeO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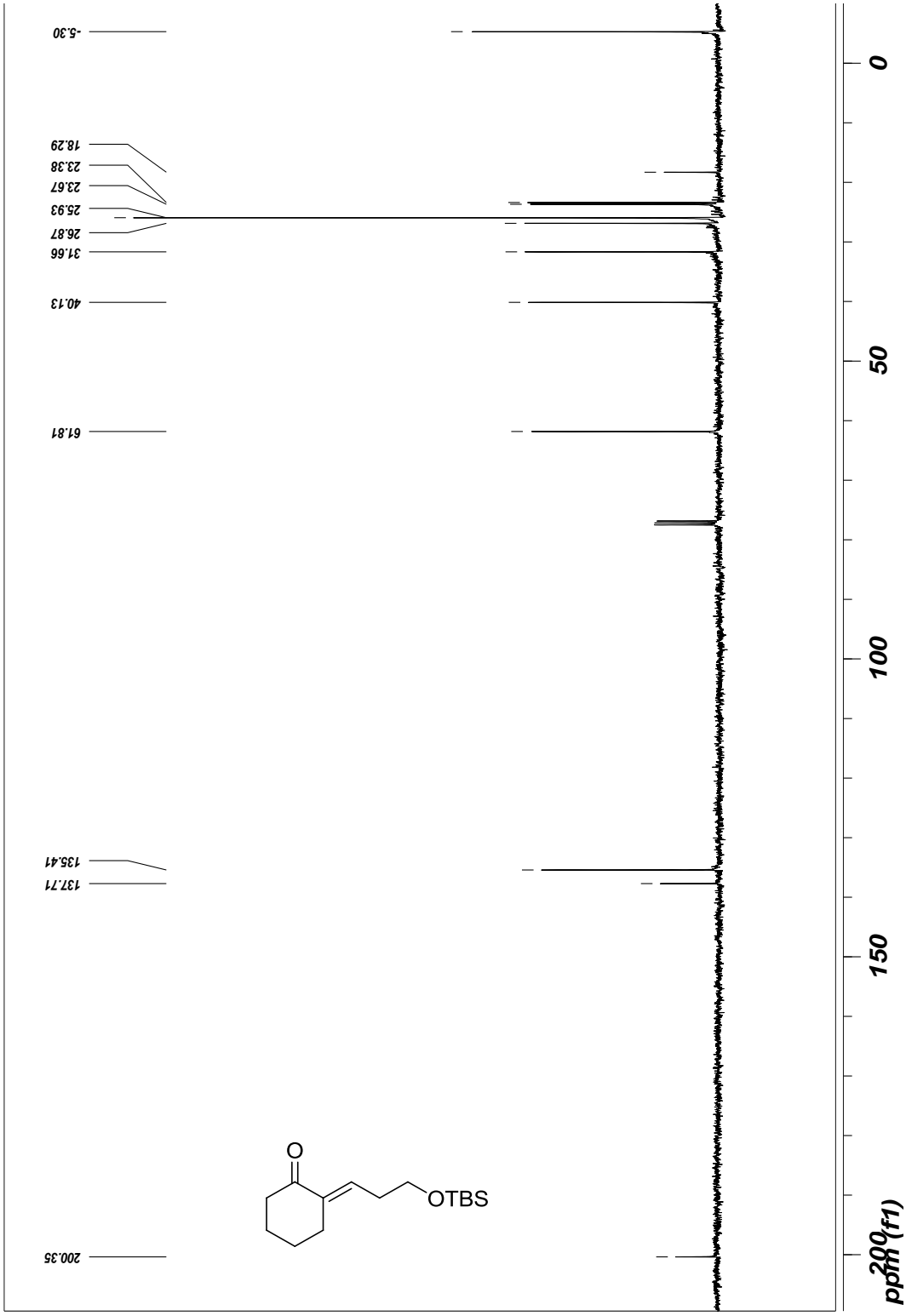
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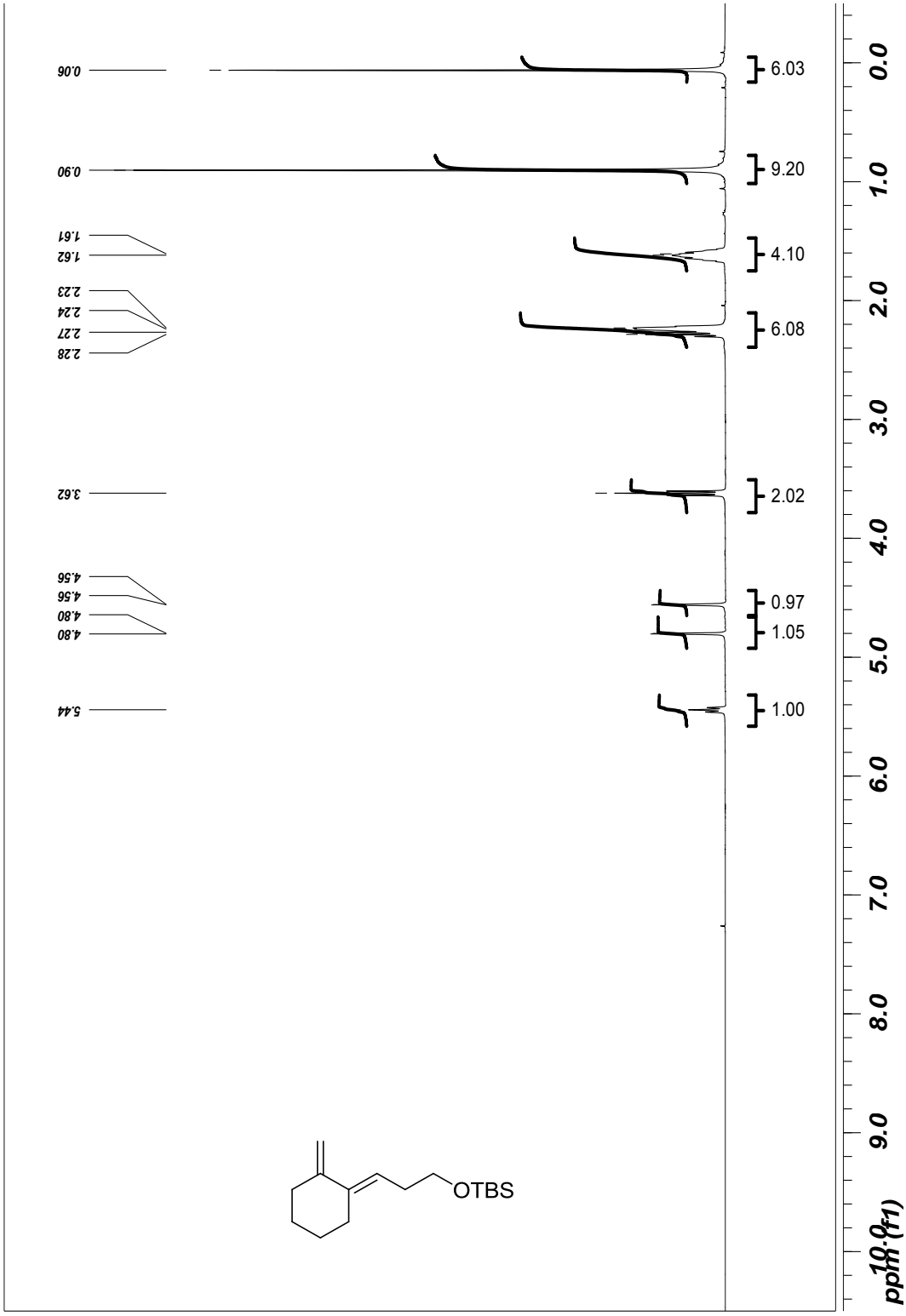
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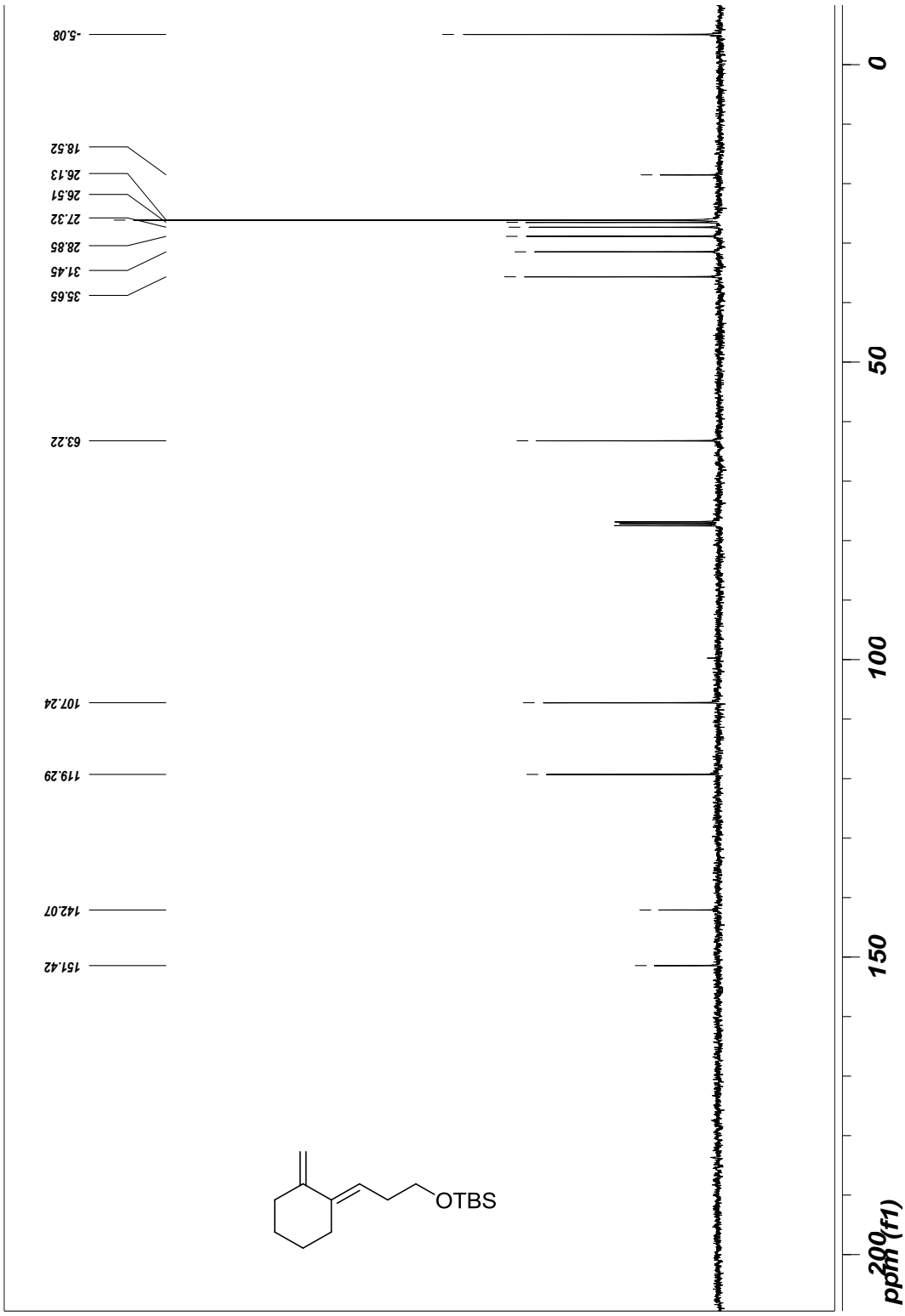
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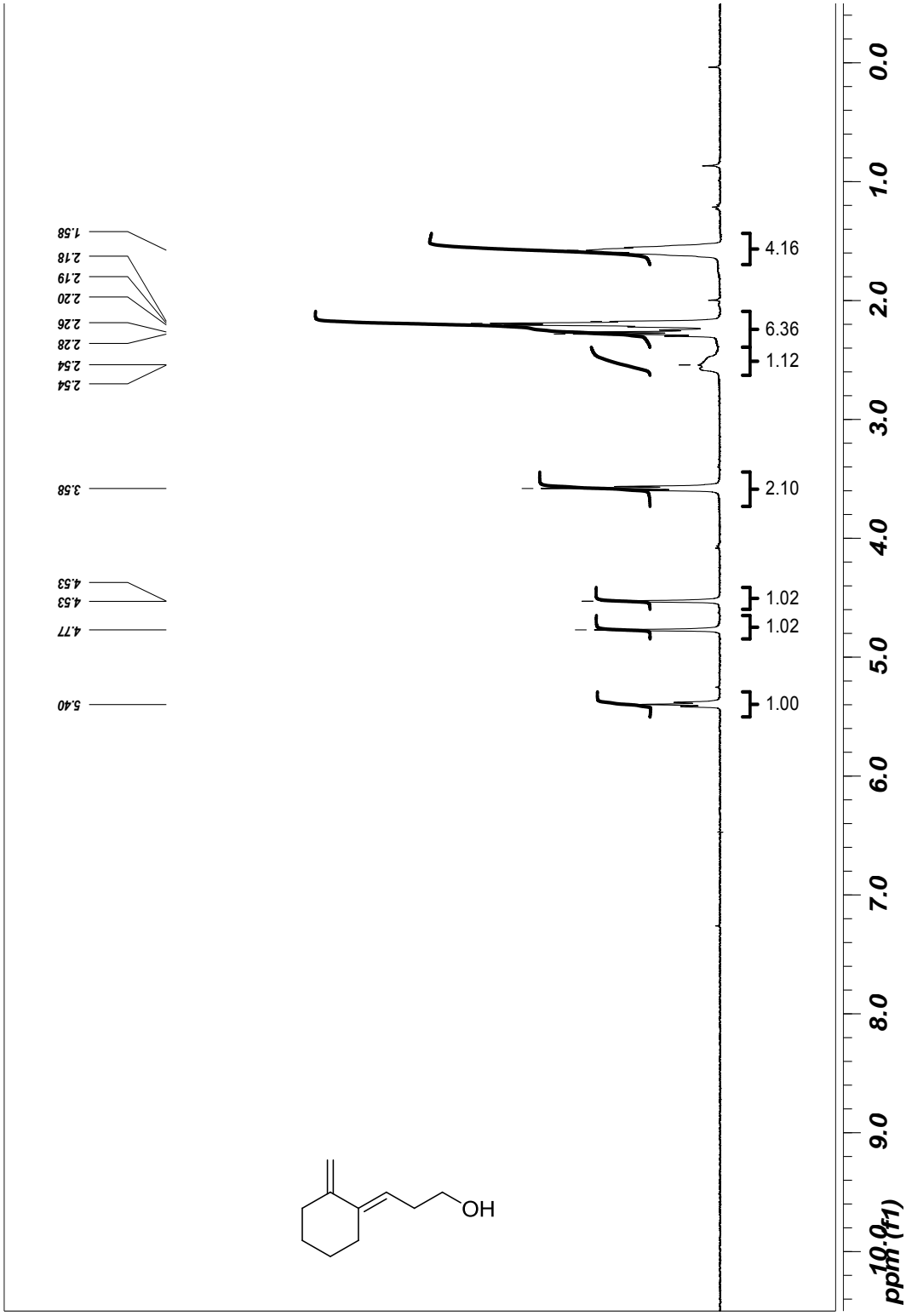
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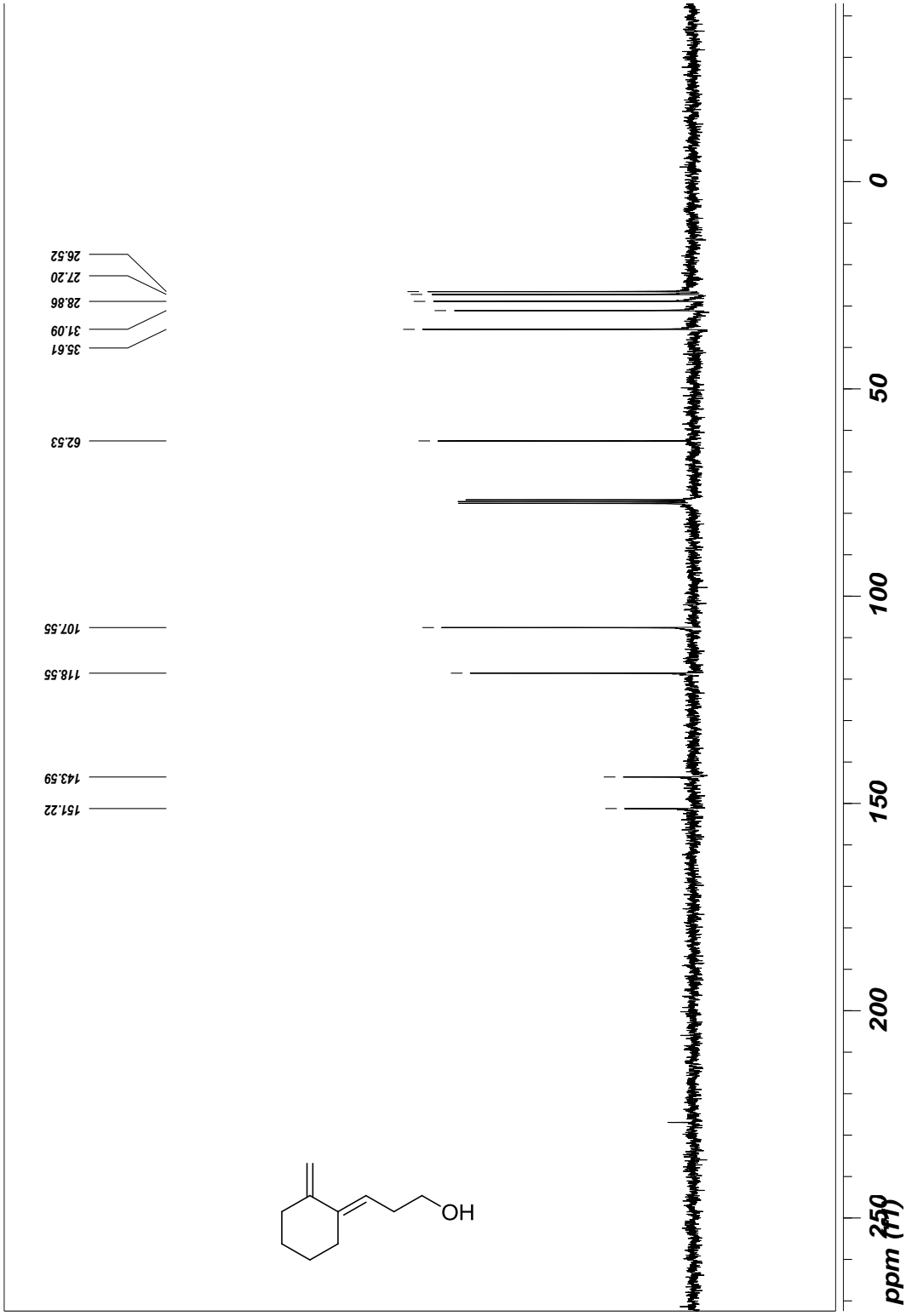
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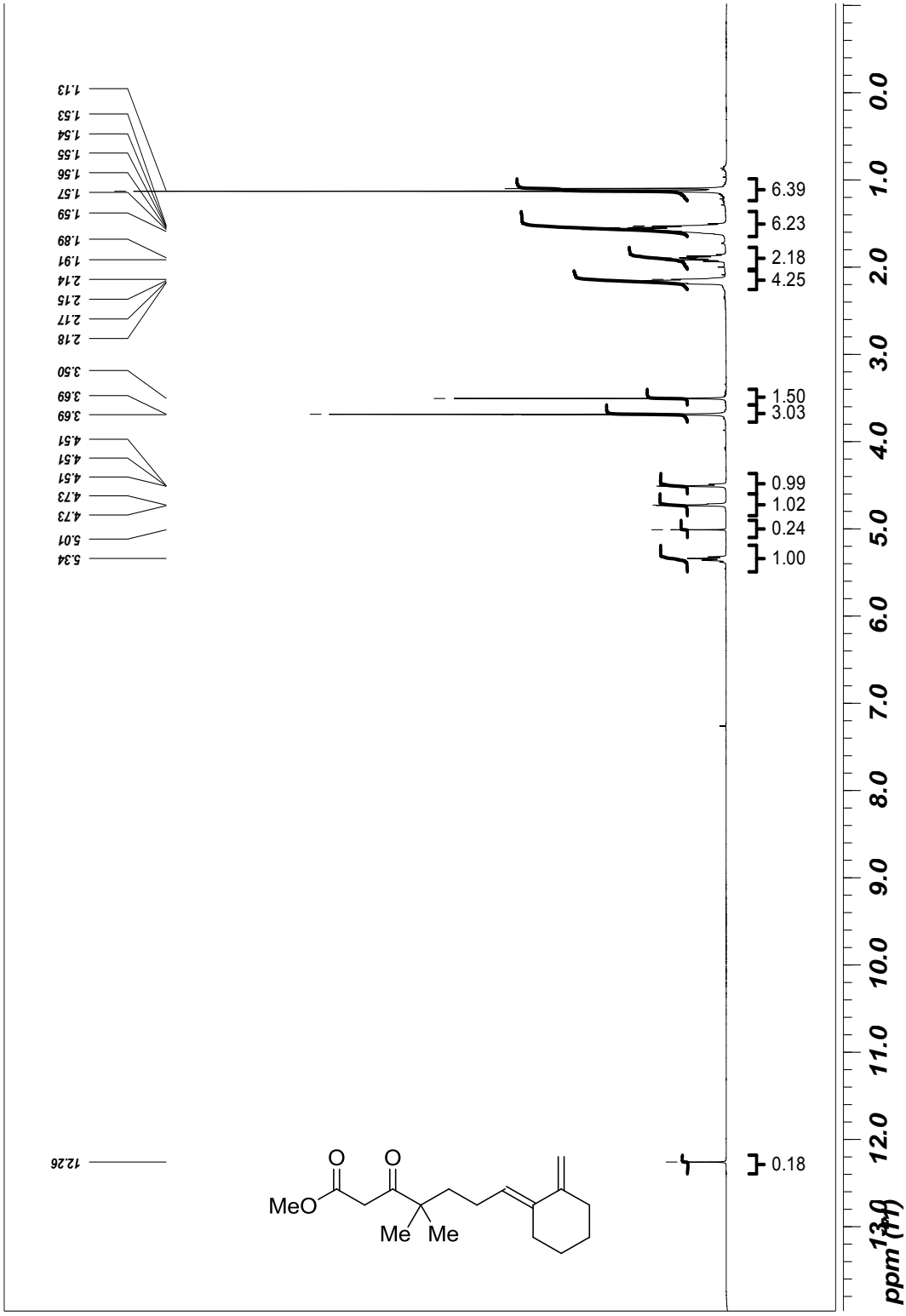
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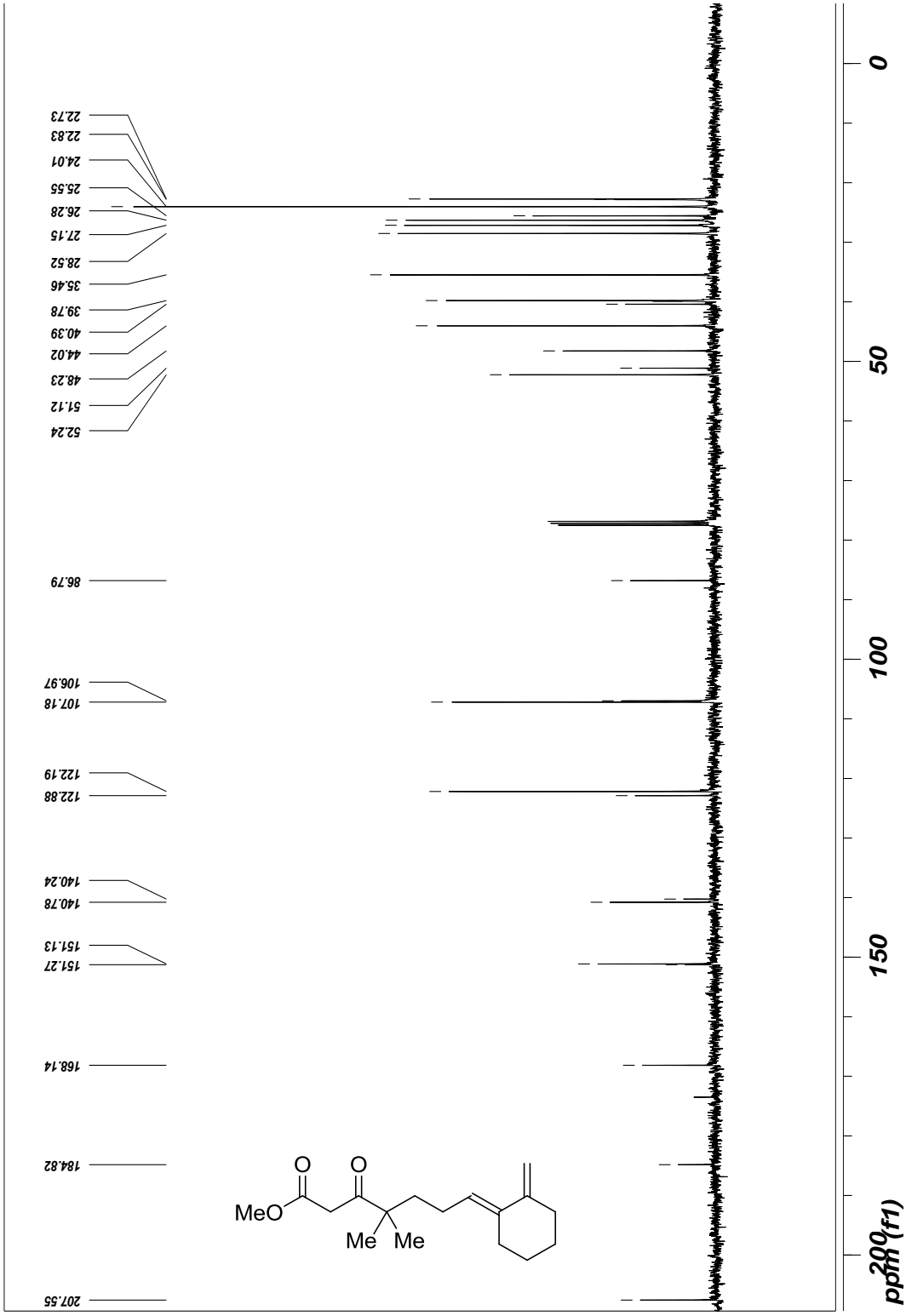
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151.13
151.27
168.14
184.82
207.55
O
O
MeO
Me
Me
0
50
100
150
200
ppm (f1)

CHAPTER 2

Development of a Formal [4+1] Cycloaddition: One Pot I_2-Mediated Intramolecular Cyclopropanation of 1,3-Dienyl β-Keto Esters and MgI_2-Promoted Vinylcyclopropane-Cyclopentene Rearrangement

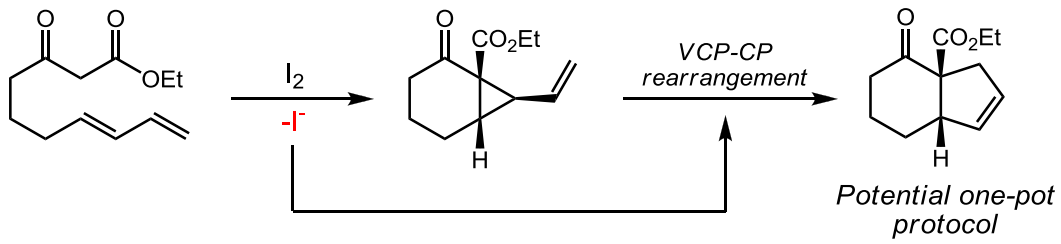
Introduction

While we were pleased with the accomplishment of realizing a palladium-catalyzed formal [4+1] cycloaddition, there were still two important ways in which we wished to improve on the reaction. We wanted to (1) expand the scope of the reaction beyond molecules containing the *gem*-dimethyl substitution and (2) realize a one-pot protocol for the [4+1] reaction protocol. When most approaches to achieving either of these goals with the palladium-catalyzed reaction protocol failed, our attention turned to other known methods of activating olefins to nucleophilic attack by carbon nucleophiles.

While a number of transition metals could conceivably be utilized for our reaction paradigm, iodine in particular appeared especially interesting. Potential advantages of an iodine-mediated protocol included relatively mild reaction conditions and low reagent cost. Iodine, in addition to serving as an activator for nucleophilic attack, could also serve as oxidant, obviating the necessity of an external oxidant.

Perhaps most intriguing, however, was the fact that if iodine were the oxidant in the oxidative vinylcyclopropanation reaction, iodide would be the reduced byproduct. In our previously reported VCP-CP rearrangement, iodide was a necessary reagent for the nucelophilic opening of our vinylcyclopropane substrates and subsequent nucleophilic displacement to form cyclopentenes.[1] If iodine were used in the initial vinylcyclopropanation reaction, we reasoned, iodide would then be available to initiate the requisite VCP-CP rearrangement in a one-pot tandem process (Figure 1). Iodine, then, would potentially be an ideal reagent for our envisioned one-pot [4+1] protocol.

Figure 1. Potential one-pot iodine-mediated vinylcyclopropanation and iodide-mediated VCP-CP rearrangement [4+1] reaction protocol.

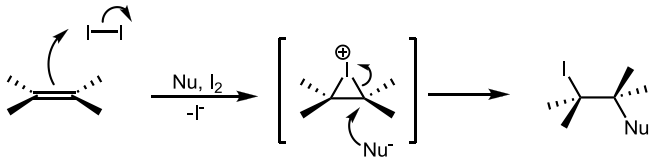


Iodine-Mediated Nucleophilic Additions

Iodine has long been known to facilitate the addition of nucleophiles to carbon-carbon double and triple bonds. Indeed, the observation of a solution of iodine losing its characteristic purple color in the presence of alkenes – an iodine-mediated addition of iodide – likely predates modern scientific literature. Insofar as we imagine the reaction to proceed, the electrons located within the π-bond of the alkene attack iodine, displacing

iodide (Figure 2). An iodonium complex is then formed in which the formal positive charge is delocalized among the three atoms of the ring. This charge distribution causes the carbons of the iodonium complex to be particularly electrophilic. A nucleophile then attacks the either of the carbons at the opposite face of the iodonium complex, resulting in an *anti* 1,2-disubstituted product.

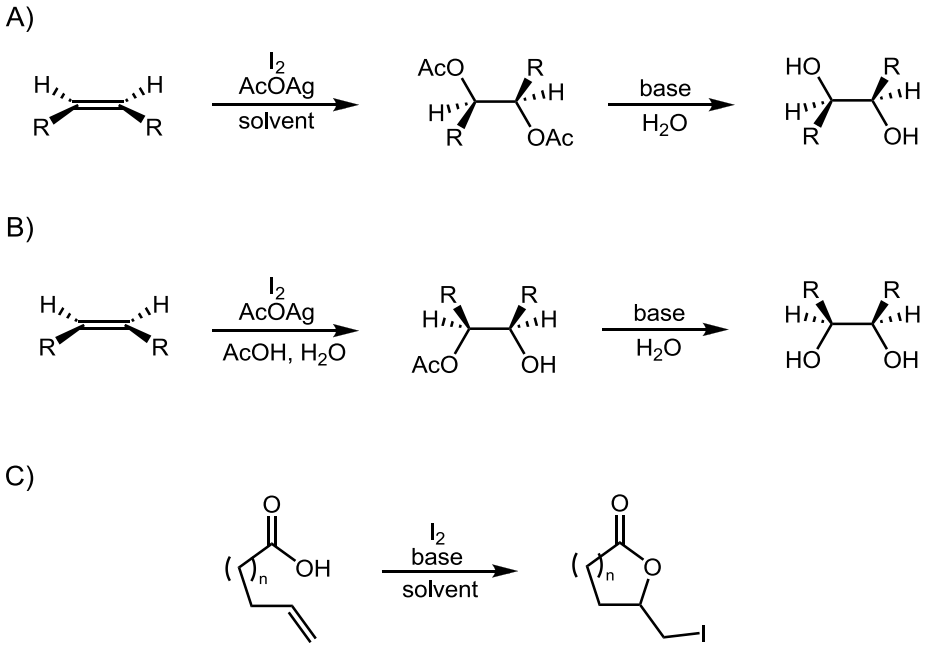
Figure 2. Mechanism of iodine-mediated addition of nucleophiles to an alkene.



The ability of iodine to facilitate the addition of nucleophiles to olefins has led to the discovery of a number of useful organic transformations. Most notably, the Prévost[2] and Woodward[3] dihydroxylations and iodolactonization[4] reactions have been indispensible tools in the synthesis of numerous useful molecules (Figure 3, A & B). The Prévost and Woodward reactions, both used for the synthesis of 1,2-diols, involve activation of an olefin by iodine – forming the aforementioned iodonium intermediate – followed by attack of an acetate ion. In the Prévost reaction, a second acetate adds to the opposite face of the initial acetate attack, forming a *trans* addition product. In the Woodward reaction, water hydrolyzes the initially added acetate, resulting in the *cis* addition product. In either reaction, the acetates are typically hydrolyzed upon treatment with base and water to furnish the corresponding 1,2-diols. Iodolactonizations involves a similar attack by carboxylate onto the iodonium complex, but occurs in an intramolecular fashion (Figure 3, C). The iodide is typically kept intact under the reaction conditions,

but may be removed by reduction in subsequent synthetic steps. Iodolactonizations have proven especially useful in several landmark natural product syntheses, such as Corey and coworker's synthesis of prostaglandins $F_{2\alpha}$ and E_2,[5] Still and coworker's synthesis of monensin,[6] and Curran and Chen's synthesis of (±)-$\Delta^{9(12)}$-capnellene.[7]

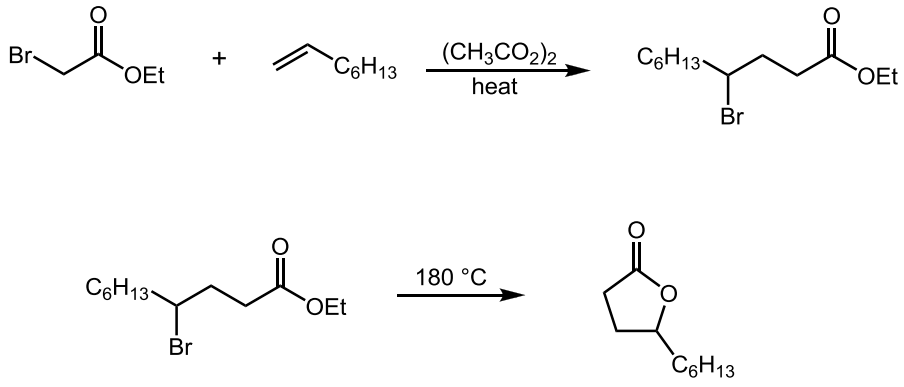
Figure 3. Common reactions involving the iodine-mediated addition of nucleophiles to olefins; A) the Prévost reaction, B) the Woodward *cis*-dihydroxylation, and C) the iodolactonization reaction.



Comparatively few reactions have involved the successful addition of carbon nucleophiles to the halonium complex. Perhaps the earliest example of a reaction following this paradigm was reported by Kharasch, Skell, and Fisher in 1948 using an α-bromoester – although the reaction proceeded by a radical chain mechanism.[8] In this seminal publication, the investigators reported the addition ethyl α-bromoacetate across

the double bond of 1-octene upon treatment of diacetylperoxide and heat (Figure 4). The group also demonstrated the cyclization of the ester onto the pendant bromide of the product under pyrolysis conditions, furnishing lactone products.

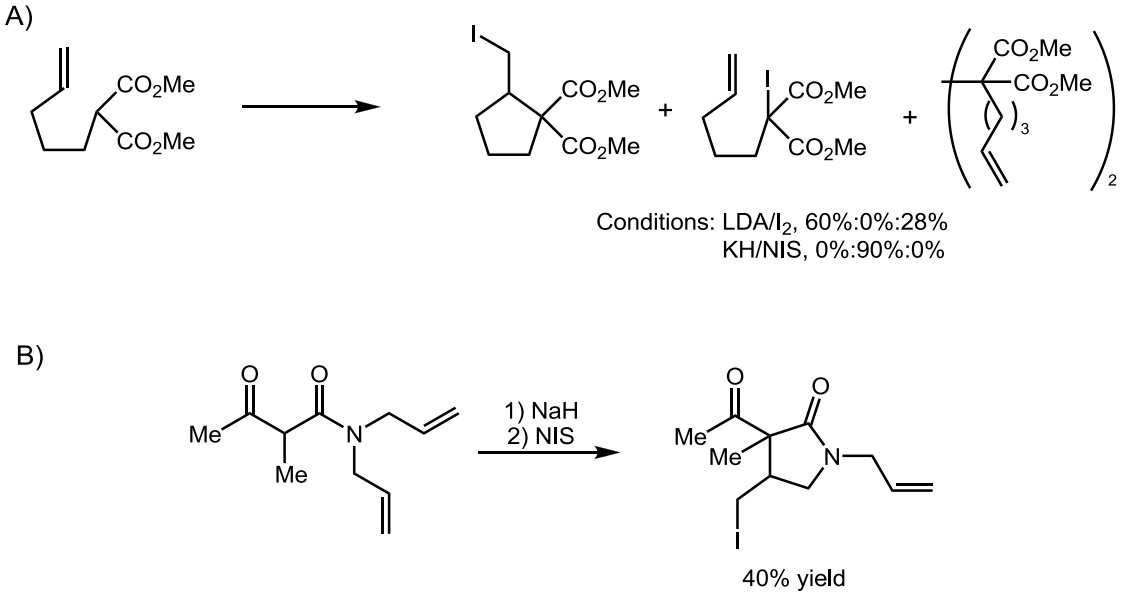
Figure 4. Kharasch, Skell, and Fisher's example of a radical addition of ethyl α-bromoacetate to an olefin and subsequent lactonization.



The first example of a simple ionic iodocarbocylization was reported by Curran and Chang in 1989.[9] While the investigation largely probed several radical iodocyclizations, the authors discovered that treatment of the lithium enolate of alkenyl malonates with iodine led primarily to the formation of cyclized products, with homocoupled products in smaller amounts (Figure 5, A). The authors were actually attempting to isolate the uncyclized iodomalonate, but instead recovered none under the reported conditions. Interestingly, using potassium hydride/N-iodosuccinimide instead of lithium diisopropylamide/I_2 led to a 90% yield of the desired iodomalonate. At the time, a mechanism was not established but the authors made note that the reaction could be occurring by either radical chain or ionic mechanisms. A similar ionic iodocarbocylization was reported by Cossy and Thelland in 1990 (Figure 5, B).[10] In this

communication, the authors reported the cyclization of β-ketoamide **X** to the corresponding cyclized product upon treatment of NaH and NIS.

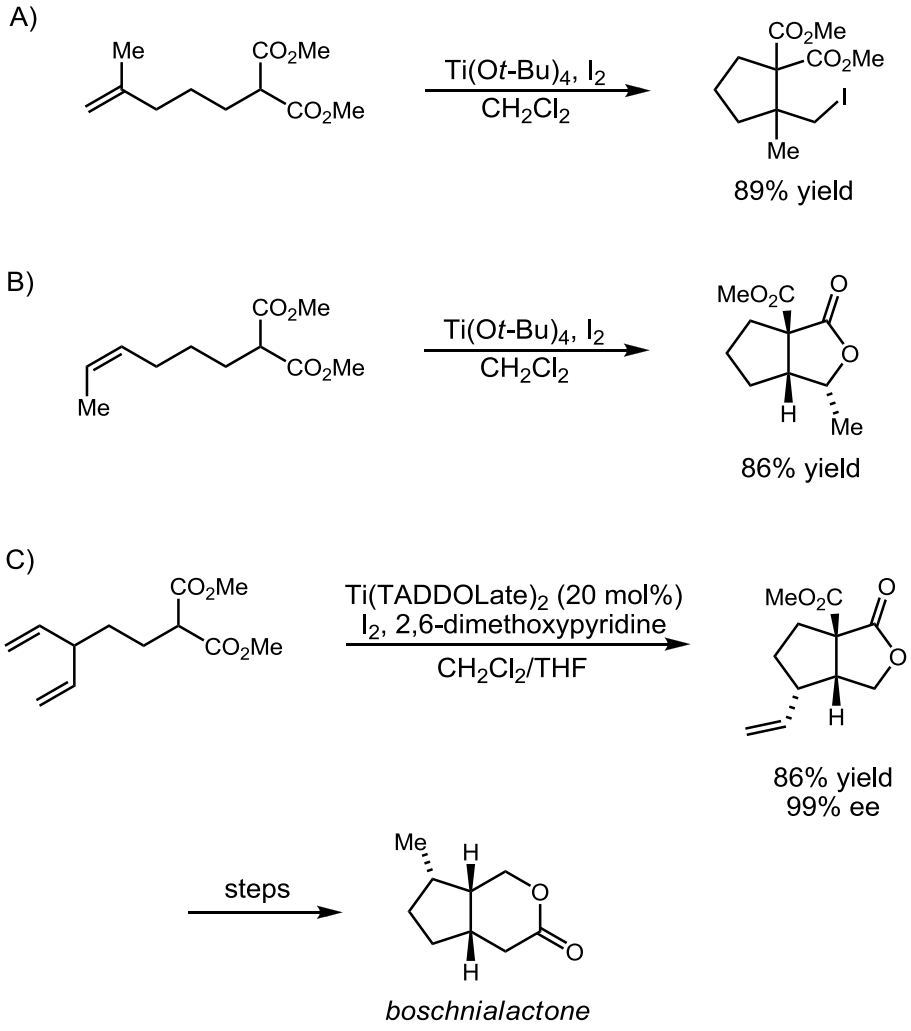
Figure 5. A) Curran's example of an ionic iodocarbocylization of malonates, and B) Cossy and Theland's example of an ionic carbocylization of β-ketoamides.



The first full investigation into the ionic iodocarbocyclization was performed by Taguchi and coworkers in 1993.[11] In the communication, the authors report a Ti(O-*t*Bu)$_4$ promoted addition of malonates onto pendant olefins activated by iodine (Figure 6, A). Employing the protocol, a number iodocarbocyclized products were reported. In addition, an interesting tandem displacement of iodide by a malonate carboxylate was also reported (Figure 6, B). This tandem process led to the construction of various doubly annulated lactone architectures. The high stereospecificity observed stood in direct contrast with the more stereorandom radical chain mechanisms previously reported, leading the authors to believe that the reaction proceeded through ionic pathways. Catalytic asymmetric

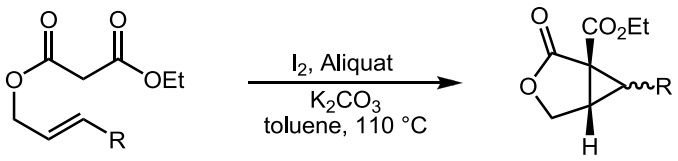
versions of the reaction were also developed by Taguchi and coworkers using TADDOLate ligands.[12] The enantioselective method was also applied to the asymmetric synthesis of boschnialactone (Figure 6, C).

Figure 6. A) Selected example of Taguchi's Ti(O-*t*Bu)$_4$-promoted iodine mediated iodocarbocylization, B) tandem iodocarboclycization lactonization reaction, and C) an asymmetric variant with tandem ester-closure used in the total synthesis of boschnialactone.



The first example of a single activated carbon species serving as both the initial iodocarbocylization nucleophile and as the nucleophile responsible for displacement of the resulting iodide was reported by Tǒke and coworkers in 1990.[13] In the investigation, treatment of alkenyl malonates with I_2 and K_2CO_3 under phase transfer conditions led to the isolation of cyclopropyl malonates (Figure 7). Further investigations revealed that the reaction likely proceeds via a carbene mechanism.[14] The loss of stereochemical integrity of the double bond, the authors suggested, was likely the result of a long-lived triplet carbene complex. Additionally, 5-enol-*endo*-exo-trig cyclizations were observed which should be disfavored according to Baldwin's rules, supporting further the carbene reaction mechanism.

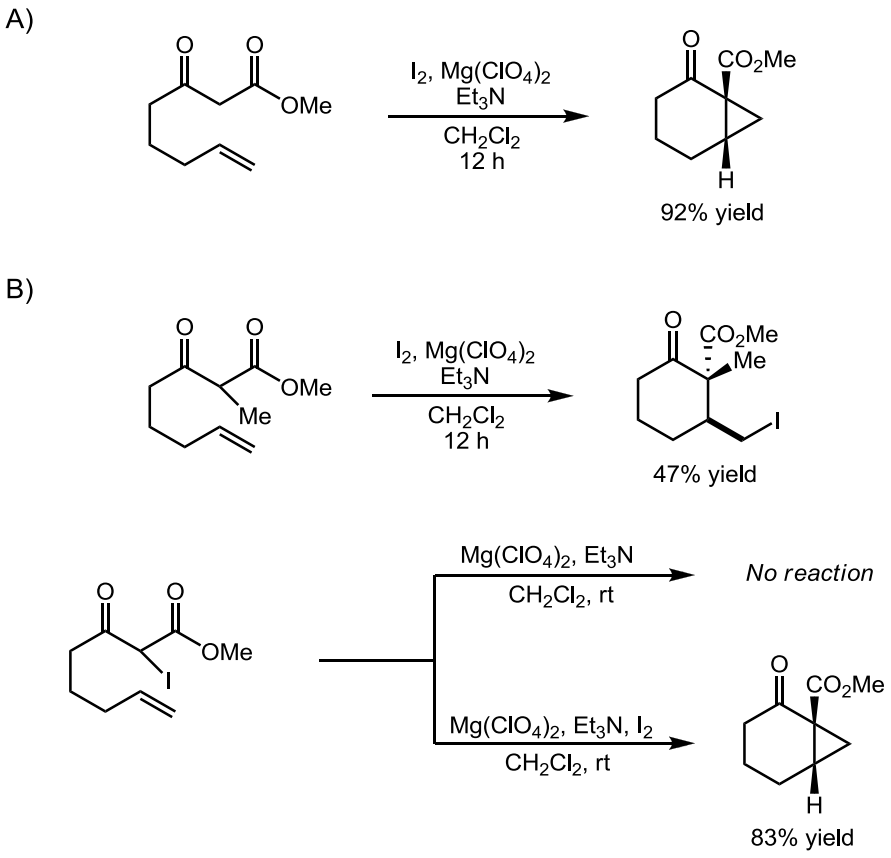
Figure 7. Tǒke and coworkers iodine-mediated carbene cyclization of malonates to form cyclopropanes.



The investigation most in line with our proposed reaction design was that of Yang and coworkers (Figure 8).[15] In this investigation, a similar cyclopropanation method to that of Tǒke and coworkers was reported. However, the mechanism in this case was ionic in nature, rather than proceeding through a carbene. The authors found that under the treatment of the magnesium perchlorate, triethylamine and iodine, alkenyl β-ketoesters cyclized cleanly to the corresponding cyclopropanes (Figure 8, A). In contrast to the reaction reported by Tǒke and coworkers, the Lewis acid-promoted

cyclopropanation proceeded with retention of the stereochemical integrity of the olefin. Furthermore, alkenyl α-methyl-β-ketoesters cyclized to the iodide containing product, suggesting that this may indeed be an intermediate in the cyclopropanation (Figure 8, B). The investigators also subjected α-iodo-β-ketoester substrates, proposed intermediates in the Tǒ ke reaction, to the reaction conditions without iodine and found no evidence of cyclized products. This observation further confirmed the ionic, rather than carbene, mechanism.

Figure 8. A) $Mg(ClO_4)_2$-promoted iodine-mediated cyclopropanation reaction developed by Yang and coworkers, and B) experimental evidence of ionic, rather than radical or carbene, pathway.

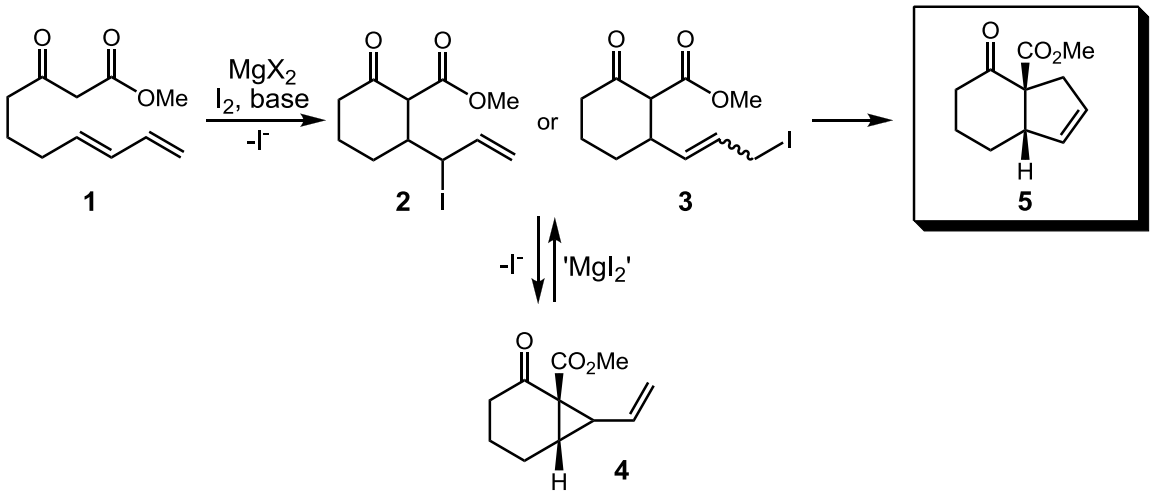


The reaction presented by Yang and coworkers, we thought, was especially attractive from the standpoint of a potential [4+1] protocol. The reaction employed a single carbon nucleophile for the construction of cyclopropanes, which would likely also proceed successfully in dienyl substrates. The reaction also exhibited good diastereocontrol, which would be important in the construction of complex cyclopentene products. Finally, the reaction was exceedingly mild, potentially offering good functional group tolerance. It was based on these reaction conditions that we approached our [4+1] reaction protocol.

Proposed Reaction Design

Given the results of Yang and Taguchi, along with our own developments for the VCP-CP rearrangement, we were confident a one-pot metal-free formal [4+1] reaction protocol could be realized (Figure 9). In the envisioned reaction scheme, iodine would activate the diene of substrate **1** for magnesium Lewis acid-promoted nucleophilic attack by the activated carbon nucleophile, forming allylic iodides **2** or **3**. Either allylic iodide could then close to cyclopentene **5** directly or to vinylcyclopropane **4**. As seen in our previous palladium-catalyzed annulation, the vinylcyclopropane would be the likely initially formed product.[1] Under the reaction conditions of the proposed vinylcyclopropanation, two equivalents of iodide are formed, effectively generating MgI_2 in the process of the reaction. Vinylcyclopropane **4**, then, could then be funneled to cyclopentene **5** upon action of the *in situ* generated MgI_2, similar to our reported VCP-CP rearrangement.

Figure 9. Proposed reaction scheme for the Lewis acid-promoted iodine-mediated [4+1] annulation protocol.



Our strategy for the realization of such a [4+1] protocol was fairly straight forward. First, conditions for which the iodine-mediated vinylcyclopropanation would take place would need to be investigated. Given Yang's previous success with the cyclopropanation of β-ketoesters onto pendant olefins, we were confident the conditions could be extended to our dienyl substrates. Having already developed a robust reaction protocol for effecting the VCP-CP rearrangement, our work would then focus on the marriage of the two reaction protocols in a single reaction pot.

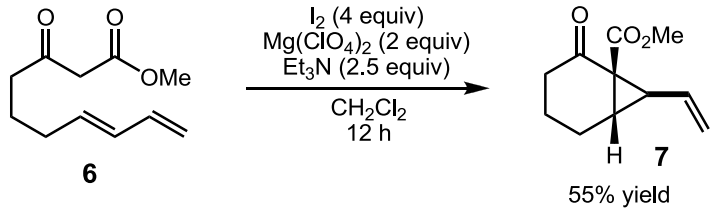
There appear to be several advantages of the proposed [4+1] reaction protocol over known procedures. To date, a practical, efficient, and robust [4+1] cyclization has yet to be realized. This would provide a valuable entry into the synthetic techniques for accessing cyclopentene structures. The reactions should also proceed in a particularly mild manner, given the previous developments by Yang and ourselves. Furthermore,

previous versions of the ionic iodocarbocylization have been shown to proceed with particularly high enantioselectivity in the presence of chiral ligands and therefore asymmetric variants would be possible with the envisioned protocol.

Results and Discussion

The first step in the realization of the envisioned [4+1] cycloaddition protocol would be to establish an effective cyclopropanation. We were fortunate in that the conditions of Yang and coworkers were, in fact, amenable to our diene system, albeit in reduced yield (Figure 10). As such, dienyl β-ketoester **6** was converted under the reaction conditions to vinylcyclopropane **7** in 55% yield. There were, however, no traces of the cyclopentene product, and therefore merging the protocols of Yang's cyclopropanation conditions and our previously reported VCP-CP rearrangement would be necessary.

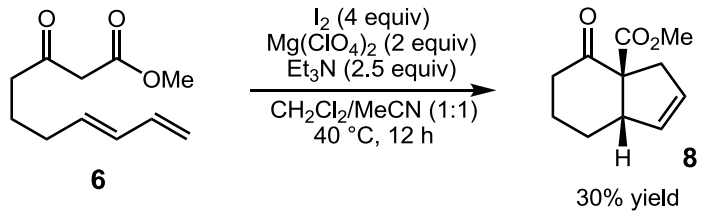
Figure 10. The first successful iodine-mediated vinylcyclopropanation.



Our initial investigations into the melding of the two reaction protocols involved changing the reaction solvent. Given that our reported VCP-CP rearrangement proceeded in acetonitrile and the new vinylcyclopropanation protocol occurred in dichloromethane,

it seemed likely that solvent was the limiting factor. Attempts to perform the vinylcyclopropanation in acetonitrile failed to generate either the vinylcyclopropane or the cyclopentene. A solvent exchange with the crude vinylcyclopropane product or simply adding acetonitrile to the reaction vessel following complete conversion to vinylcyclopropane also failed. Our first success at performing the iodine-mediated one-pot formal [4+1] protocol was quickly realized, however, by using a combination solvent system (Figure 11). Employing equal parts dichloromethane and acetonitrile at elevated temperatures, diene substrate **6** was converted to cyclopentene **8** in reasonable yield.

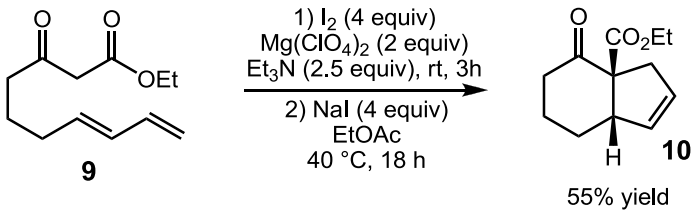
Figure 11. First example of a one-pot Lewis acid-promoted iodine-mediated vinylcyclopropanation and tandem VCP-CP rearrangement resulting in formal [4+1] adducts.



It was found that in the combination solvent system, a considerable amount of decomposition was observed. A solvent screen revealed that ethyl acetate allowed both reactions to occur in a much more clean manner, albeit similar yields of product. Analysis by TLC and ^{1}H NMR under the new reaction conditions showed that the reaction was indeed forming the vinylcyclopropane first, and that failure to convert completely to the cyclopentene product was the factor limiting the yield of the overall reaction. It was hypothesized that the two equivalents of iodide created in the reaction

were not sufficient to facilitate the VCP-CP rearrangement. During the course of the reaction, up to two equivalents of iodide could be formed while there were two equivalents of magnesium perchlorate. The ratio of iodide to magnesium cations was less than that of our previously reported conditions and therefore the VCP-CP rearrangement could be retarded as a consequence. Unfortunately, adding additional equivalents of sodium iodide at the beginning of the reaction resulted in complete inhibition of the vinylcyclopropanation. Adding four equivalents of sodium iodide after the vinylcyclopropanation reaction had completed, however, led to a dramatically increased yield of the cyclopentene product (Figure 12). As such, subjecting diene substrate **9** to the original reaction conditions at room temperature for three hours, followed by the addition of four equivalents of sodium iodide and heating for 18 hours, cyclopentene **10** was isolated in the 55% yield. Under the new reaction protocol, no remaining vinylcyclopentene was observed upon completion of the reaction.

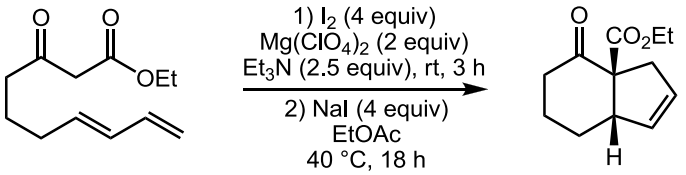
Figure 12. Employing additional iodide following completion of vinylcyclopropanation in two-part one-pot [4+1] protocol.



Having a reaction protocol in place that sufficiently converted our dienyl substrate to vinylcyclopropane, and then the vinylcyclopropane to cyclopentene, optimization of the reaction was then pursued. A concentration screen revealed that, in general, more

dilute reaction conditions led to high yields (Table 1). The 0.025 M concentration (entry 3) was carried forward as higher dilutions became impractical and resulted in only marginal increases in yield. The more dilute reaction conditions likely disfavor undesired intermolecular decomposition pathways.

Table 1. Concentration effects of the iodine-mediated [4+1] reaction protocol.

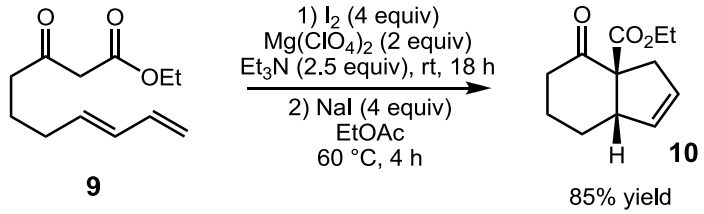


entry	conc. (M)	yield (%)
1	0.1	53
2	0.05	55
3	0.025	60
4	0.01	62

Further increases in yield were observed by careful optimization of reaction times. It was discovered that while the starting material is consumed very quickly under the reaction conditions, not all was converted to the vinylcyclopropane. Consistent with the observations by Yang and Coworkers, the β-ketoester substrate appeared to be in equilibrium with the the α-iodo compound with a majority of material converting to the α-iodo compound in a matter of minutes. It was found then that increasing the reaction time of the first step to 18 hours led to an increase in yield. The longer reaction time allowed sufficient time for the vinylcyclopropanation to occur. Having elucidated this part of the mechanism, it came to our attention that the second step actually occurred on faster time scales than initially thought, reaching completion in under four hours at 60 °C. These changes in reaction time led to sufficiently optimized reaction conditions (Figure

13). In the optimized reaction conditions, the dienyl β-ketoester substrate **9** is subjected to treatment of two equivalents magnesium perchlorate, four equivalents of iodine, and 2.5 equivalents of triethylamine at room temperature for 18 hours. Four equivalents of sodium iodide are added and the reaction is heated to 60 °C for 4 hours. These optimized reaction conditions led to an 85% isolated yield of desired cyclopentene **10**.

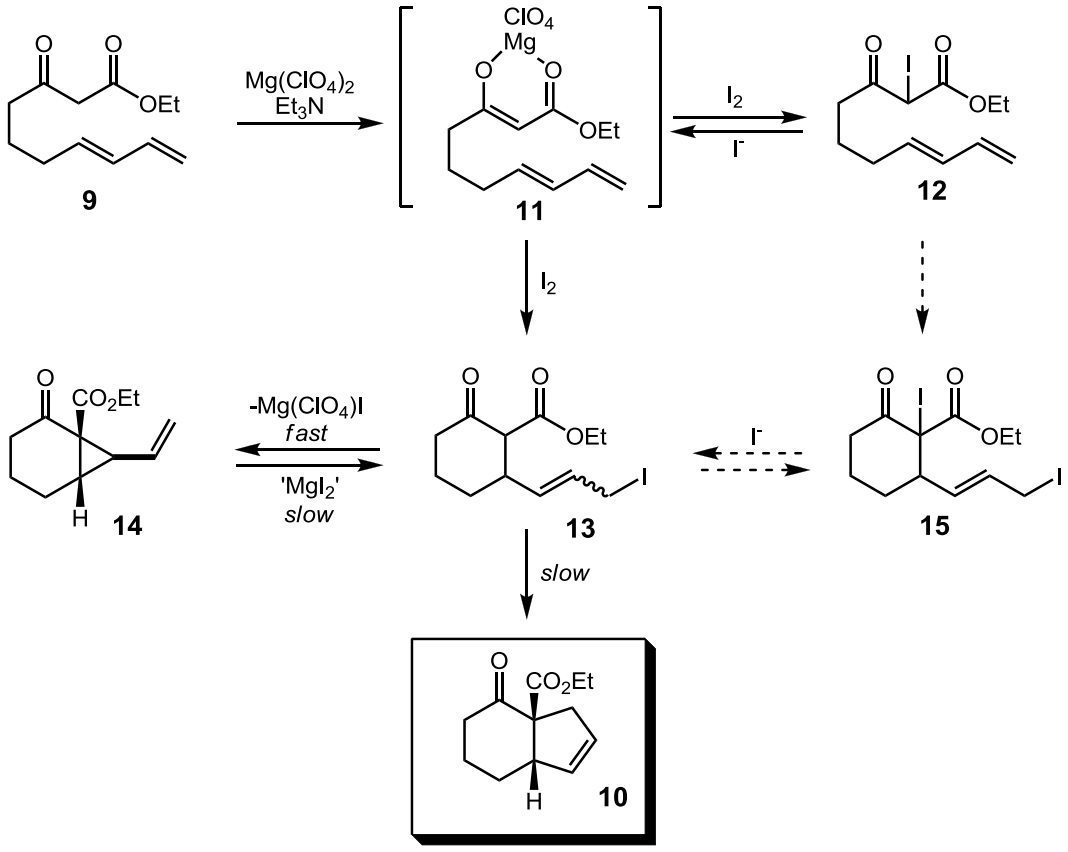
Figure 13. Optimized reaction conditions of the $Mg(ClO_4)_2$-promoted iodine mediated [4+1] annulation protocol.



Based on our observations of the reaction progression, the proposed mechanism for the reaction is presented in Figure 14. Upon treatment with magnesium perchlorate and triethylamine, diene substrate **9** is converted to magnesium enolate **11**. Magnesium enolate **11**, upon interaction with iodine, establishes a rapid equilibrium with α-iodo compound **12**. This equilibrium mixture is slowly converted to the annulated allylic iodide product **13**. Intramolecular ring closure of the allylic iodide occurs quickly to form vinylcyclopropane **14**. The vinylcyclopropane is slowly and reversibly converted back to allylic iodide intermediate **13**, the rate of which is greatly enhanced by the addition of sodium iodide. Desired cyclopentene **10** is slowly and irreversibly formed by the competing 5-*exo* ring closure of the allylic iodide intermediate. As yet, we cannot rule out the possibility of closure of α-iodo compound **12** directly to furnish the α-iodo

intermediate **15,** followed by deiodination to reach common allylic iodide intermediate **13**.

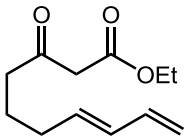
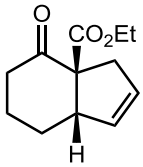
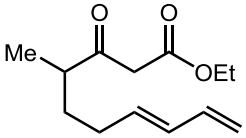
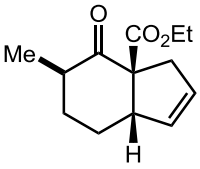
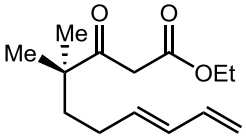
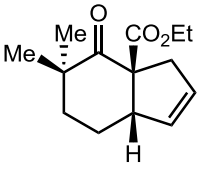
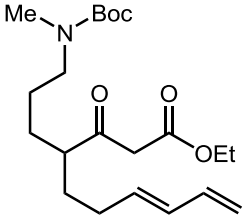
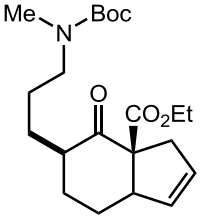
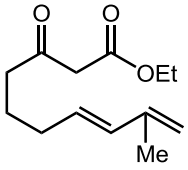
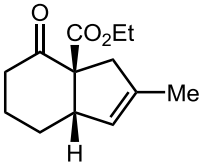
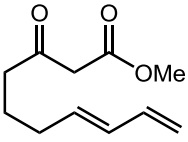
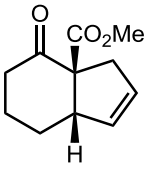
Figure 14. Proposed reaction mechanism for the $Mg(ClO_4)_2$-promoted iodine-mediated [4+1] annulation protocol.



Having achieved the one-pot [4+1] reaction protocol in the model substrate, we then investigated the scope of newly developed reaction (Table 2). The reaction proceeded with a high amount of stereocontrol in the case δ-methyl substrates, giving a 69% yield of the desired cyclopentene with a 10:1 d.r. (entry 2). The δ-dimethyl substituted substrate also proceeded efficiently to cyclopentene (entry 3). The presence

of BOC-protected amine groups were readily tolerated under the reaction conditions with no significant loss of yield (entry 4). Substitution on the internal position of the terminal diene was readily accommodated (entry 5), albeit at a reduced yield. Finally, methyl esters were amenable to the reaction protocol (entry 7), but yields were less than that of the ethyl ester substrates. This could potentially be due to unfavorable Krapcho-like reaction side products.

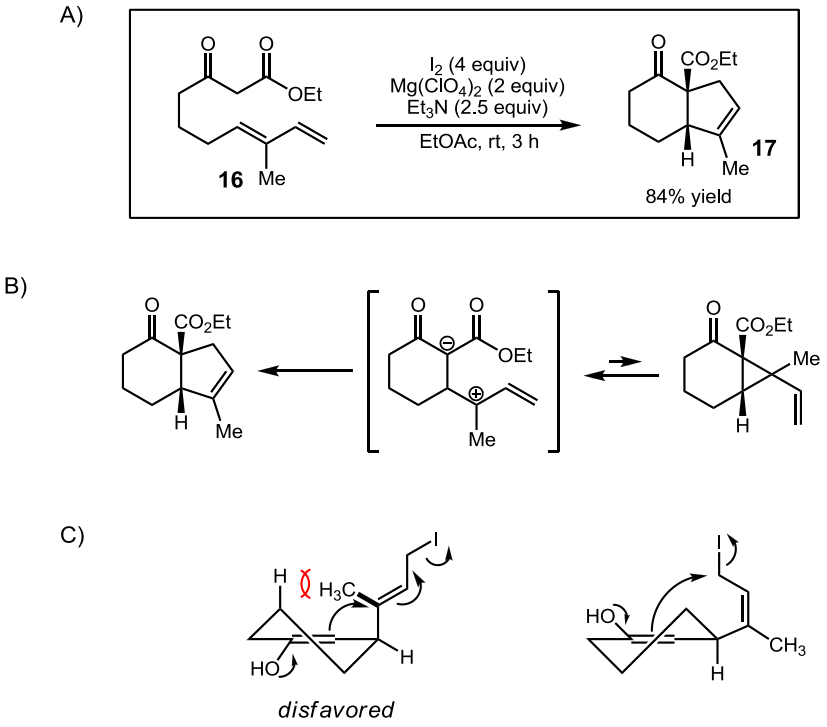
Table 2. Substrate scope of $Mg(ClO_4)_2$-promoted iodine-mediated [4+1] annulation protocol.[a]

Entry	Substrate	Product	% Yield	d.r.
1			85	--
2			69	10:1
3			79	--
4			71	>10:1
5			47	--
6			42	--

[a] All reactions carried out in two phases. Phase one: substrate (50 mg), I_2 (4 equiv), $Mg(ClO_4)_2$ (2 equiv), Et_3N (2.5 equiv) in EtOAc (0.025 M with respect to substrate) were stirred at rt for 18 h. Phase two: NaI (4 equiv) was added and reaction mixture was heated to 60 °C for 4 hours.

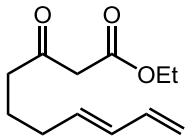
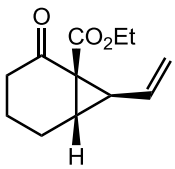
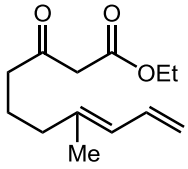
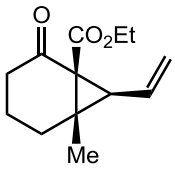
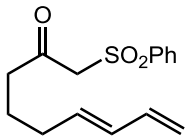
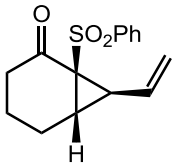
We were surprised to find that methyl-substitution on the internal diene led directly to the cyclopentene product with the need for additional heating or added iodide (Figure 15, A). Accordingly, diene substrate **16** was converted cleanly to cyclopentene **17** under the typical reaction conditions in only three hours at room temperature in 84% yield. Although we can't rule out the possibility of a transiently formed vinylcyclopropane, there was no evidence of such a species during the reaction by ^{1}H NMR or thin layer chromatography. As far as we know, this represents only the second direct carbogenic [4+1] cycloaddition of linear dienes – the first of which was presented by Spino.[16] There exist two potential explanations for the direct [4+1] cyclization – one electronic and one steric. Similar to the case presented by Spino, the reaction could proceed directly to cyclopentene due to the unusually unstable cyclopentene intermediate (Figure 15, B). The vinylcyclopropane, insofar that it forms, could quickly undergo heterolytic bond cleavage to give a stable formal zwitterionic intermediate. The positive charge of the zwitterions would be stabilized by the tertiary nature of the carbon and the adjacent vinyl group whereas the negative charge would be stabilized by the two carbonyls of the β-ketoester. In the steric argument, the requisite pseudo-axial orientation of the allyl iodide intermediate is disfavored due to interactions between the methyl substitution and the axial hydrogen as shown (Figure 15, C). Instead, the reaction proceeds to form the cyclopentene directly via a pseudo-equatorial conformation that lacks the unfavorable diaxial strain.

Figure 15. A) A $Mg(ClO_4)_2$-promoted iodine-mediated direct [4+1] cyclization, B) electronic rationale for direct [4+1] cyclization, and C) steric rationale for direct [4+1] cyclization.



We also investigated the vinylcyclopropanation reaction for our model substrate and for several substrates that did not successfully undergo the one-pot VCP-CP rearrangement (Table 3). By simply carrying out the reaction at room temperature without the addition of sodium iodide, the vinylcyclopropane of our model compound was isolated in 63% yield (entry 1). Substitution at the most internal position of the diene resulted in a vinylcyclopropane exhibiting two contiguous stereocenters with good diastereocontrol, albeit in lower yields (entry 2). Finally, a β-ketosulfone underwent the vinylcyclopropanation as well, showing an important example that other activated carbon nucleophiles could be used in the reaction (entry 3).

Table 3. Substrate scope of $Mg(ClO_4)_2$-promoted iodine-mediated vinylcyclopropanation of activation carbon nucleophiles.[a]

Entry	Substrate	Product	% Yield	d.r.
1			63	>20:1
2			37	>20:1
3			37	>20:1

[a] All reactions were carried out with substrate (50 mg), I_2 (4 equiv), $Mg(ClO_4)_2$ (2 equiv), Et_3N (2.5 equiv) in EtOAc (0.025 M with respect to substrate) at rt for 18 h.

Concluding Remarks

We have developed a mild $Mg(ClO_4)_2$-promoted iodine mediated [4+1] annulation protocol. The protocol employs an iodine-mediated vinylcyclopropanation followed by an iodide-mediated VCP-CP rearrangement in a single reaction pot. The protocol obviates the need of the *gem*-dimethyl substitution of our previous palladium-catalyzed reaction protocol. This process has proven to be particularly efficient in the synthesis of substituted dienyl β-ketoester substrates. The reaction protocol provides a mild and efficient entry into the synthesis of complex cyclopentene ring structures.

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Supporting Information

General Information:

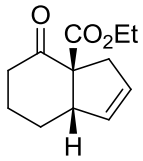
All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred by syringe under argon. Organic solutions were concentrated using a Buchi rotary evaporator. Diethyl ether, tetrahydrofuran, and methylene chloride (CH_2Cl_2) were dried using a J.C. Meyer solvent purification system. Triethylamine (Et_3N) and diisopropylamine were freshly distilled over CaH_2 under argon. All other commercial reagents were used as provided. Flash column chromatography was performed employing 32-63 μm silica gel (Dynamic Adsorbents Inc). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (EMD).

^1H and ^{13}C NMR were recorded in $CDCl_3$ on Bruker DRX-300, DRX-400, and DRX-500 spectrometers as noted. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet Avatar 370 DTGS (Thermo) using NaCl salt plates. Mass spectra (MS) were acquired on a JEOL JMS-LCmate liquid chromatography mass spectrometer system using the APCI+ technique.

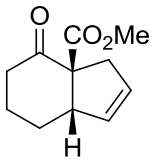
Experimental Procedures:

General Procedure A – Synthesis of Cyclopentenes: $Mg(ClO_4)_2$ was added to a 25 mL round-bottom flask and purged three times with argon. EtOAc was added (0.02 M with respect to diene), followed by the diene, iodine, and triethylamine. The reaction mixture was then allowed to stir at room temperature for 18 h. Sodium iodide was then added and the reaction mixture was heated to 60 °C and stirred for an additional 6 h. The reaction mixture was diluted to five times the original volume with EtOAc and washed successively with saturated $Na_2S_2O_3$ solution and brine (volumes equivalent to reaction volume), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the title cyclopentene.

General Procedure B – Synthesis of Vinylcyclopropanes: $Mg(ClO_4)_2$ was added to a 25 mL round-bottom flask and purged three times with argon. EtOAc was added (0.02 M with respect to diene), followed by the diene, iodine, and triethylamine. The reaction was then allowed to stir at room temperature for 18 h. The reaction mixture was diluted to five times the original volume with EtOAc and washed successively with saturated $Na_2S_2O_3$ solution and brine (volumes equivalent to reaction volume), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the title vinylcyclopropane.

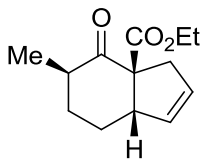


(±)-(3*S*,7*S*)-Ethyl 7-oxo-3,4,5,6,7,7-hexahydro-1H-indene-7-carboxylate: Prepared according to general procedure A from (*E*)-ethyl 3-oxoundeca-8,10-dienoate (50 mg, 0.24 mmol), $Mg(ClO_4)_2$ (106 mg, 0.47 mmol), I_2 (226 mg, 0.98 mmol), NEt_3 (83 μL, 0.60 mmol), and NaI (0.143 g, 0.98 mmol). The crude residue was purified by flash chromatography (10 % EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (42 mg, 0.20 mmol, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 1H, C**H**=CH), 5.47 (m, 1H, CH=C**H**), 4.16 (m, 2H, OC**H$_2$**CH$_3$), 3.62–3.52 (m, 1H, C**H**), 3.20–3.07 (m, 1H, C**H$_2$**CH=CH), 2.87–2.74 (m, 1H, C**H$_2$**CH=CH), 2.59–2.31 (m, 2H, C**H$_2$**C=O), 2.13–1.96 (m, 1H, C**H$_2$**CH$_2$), 1.94–1.59 (m, 3H, C**H$_2$**CH$_2$), 1.24 (t, *J* = 6 Hz, 3H, OCH$_2$C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 208.2, 171.9, 132.5, 129.9, 65.2, 61.4, 51.6, 39.7, 39.2, 26.7, 21.5, 14.0; IR (thin film) 2938, 2868, 1737, 1712, 1448, 1234, 1158, 1093, 1034 cm^{-1}; MS (APCI+) *m/z* = 209.12 calc'd for $C_{12}H_{17}O_3$ [MH]+, found 209.26.



(±)-(3*S*,7*S*)-Methyl 7-oxo-3,4,5,6,7,7-hexahydro-1H-indene-7-carboxylate: Prepared according to general procedure A from (*E*)-methyl 3-oxoundeca-8,10-dienoate (50.0 mg, 0.255 mmol), $Mg(ClO_4)_2$ (114 mg, 0.510 mmol), I_2 (259 mg, 1.02 mmol), NEt_3 (89 μL,

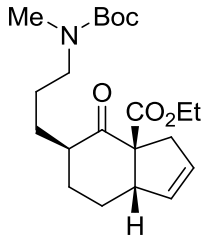
0.64 mmol), and NaI (0.153 g, 1.02 mmol). The crude residue was purified by flash chromatography (10 % EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (21 mg, 0.11 mmol, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.67 (m, 1H, C**H**=CH), 5.52–5.45 (m, 1H, CH=C**H**), 3.71 (s, 3H, OC**H$_3$**), 3.64–3.54 (m, 1H, C**H**), 3.19–3.08 (m, 1H, C**H$_2$**CH=CH), 2.88–2.77 (m, 1H, C**H$_2$**CH=CH), 2.57–2.33 (m, 2H, C**H$_2$**C=O), 2.13–1.96 (m, 1H, C**H$_2$**CH$_2$), 1.94–1.54 (m, 3H, C**H$_2$**CH$_2$); ^{13}C NMR (100 MHz, CDCl3) δ 208.2, 172.5, 132.6, 129.9, 65.2, 57.6, 51.6, 39.7, 39.3, 26.7, 21.6; IR (thin film) 2950, 2866, 1740, 1713, 1435, 1243, 1158, 1095 cm^{-1}; MS (APCI+) *m/z* = 195.10 calc'd for $C_{11}H_{15}O_3$ [MH]+, found 195.25.



(±)-(3*S*,6*R*,7*S*)-Ethyl 6-methyl-7-oxo-3,4,5,6,7,7-hexahydro-1H-indene-7-carboxylate: Prepared according to general procedure A from (*E*)-ethyl 4-methyl-3-oxoundeca-8,10-dienoate (50.0 mg, 0.223 mmol), $Mg(ClO_4)_2$ (100 mg, 0.446 mmol), I_2 (226 mg, 0.892 mmol), NEt_3 (78 μL, 0.558 mmol), and NaI (134 mg, 0.894 mmol). The crude residue was purified by flash chromatography (10 % EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (34 mg, 0.15 mmol, 69% yield, 10:1 d.r. by NMR)[1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.61 (m, 2H, C**H**=C**H**), 5.30 (s, 2H, C**H**=C**H** minor diastereomer), 4.17 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH$_3$), 3.58–3.42 (m, 1H, C**H**), 3.12 (d, *J* = 18 Hz, 1H, C**H$_2$**CH=CH), 2.73 (d, *J* = 18 Hz, 1H, C**H$_2$**CH=CH), 2.49–

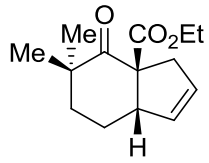
[1] Major diastereomer determined by COSY and NOESY. All others by analogy.

2.30 (m, 1H, C**H**C=O), 2.18–2.01 (m, 1H, C**H$_2$**CH$_2$), 2.01–1.84 (m, 1H, C**H$_2$**CH$_2$), 1.66–1.49 (m, 1H, C**H$_2$**CH$_2$), 1.39–1.19 (m, 4H, C**H$_2$**CH$_2$ + OCH$_2$C**H$_3$**), 1.14 (d, *J* = 6 Hz, 3H, C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 211.6, 172.8, 133.7, 128.3, 65.0, 61.4, 51.9, 42.8, 39.4, 30.2, 28.1, 16.1, 14.0; IR (thin film) 2978, 2935, 2864, 1739, 1703, 1454, 1272, 1219, 1202, 1153, 1097, 1042 cm^{-1}; MS (APCI+) *m/z* = 223.13 calc'd for $C_{13}H_{19}O_3$ [MH]+, found 223.29.

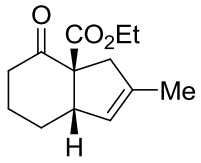


(3S,6S,7S)-Ethyl 6-(3-(tert-butoxycarbonyl(methyl)amino)propyl)-7-oxo-3a,4,5,6,7,7a-hexahydro-1H-indene-7a-carboxylate: Prepared according to general procedure A from tert-butyl propyl(methyl)carbamate diene substrate (50.0 mg, 0.131 mmol), $Mg(ClO_4)_2$ (58.0 mg, 0.262 mmol), I_2 (133 mg, 0.524 mmol), NEt_3 (46 μL, 0.33 mmol), and NaI (79.0 mg, 0.524 mmol). The crude residue was purified by flash chromatography (20 % EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (35 mg, 0.092 mmol, 70% yield, >10:1 d.r. by NMR). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71–5.59 (m, 2H, C**H**=C**H**), 4.17 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH$_3$), 3.58–3.42 (m, 1H, C**H**), 3.26–3.12 (m, 2H, NC**H$_2$**), 3.06 (d, *J* = 18 Hz, 1H, C**H$_2$**CH=CH), 2.82 (s, 3H, C**H$_3$**N), 2.80 (d, *J* = 18 Hz, 1H, C**H$_2$**CH=CH), 2.39–2.23 (m, 1H, C**H**C=O), 2.18–2.03 (m, 1H, C**H$_2$**CH$_2$), 2.03–1.87 (m, 1H, C**H$_2$**CH$_2$), 1.81–1.66 (m, 1H, C**H$_2$**CH$_2$), 1.64–1.48 (m, 3H, C**H$_2$**CH$_2$), 1.44 (s, 9H, C(C**H$_3$**)$_3$), 1.39–1.19 (m, 5H, C**H$_2$**CH$_2$ + OCH$_2$C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 210.5, 172.6, 155.8, 133.6, 128.3, 79.2, 65.1, 61.4, 51.7, 48.8, 47.6,

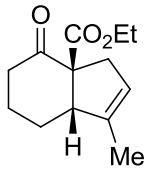
39.6, 34.1, 28.5, 27.8, 27.7, 25.4, 14.0; IR (thin film) 2933, 1739, 1695, 1453, 1394, 1365, 1229, 1158, 1114, 879 cm^{-1}; MS (APCI+) *m/z* = 380.24 calc'd for C21H34NO5 [MH]+, found 380.21.



(±)-(3*S*,7*S*)-Ethyl 6,6-dimethyl-7-oxo-3,4,5,6,7,7-hexahydro-1H-indene-7-carboxylate: Prepared according to general procedure A from (*E*)-ethyl 4,4-dimethyl-3-oxoundeca-8,10-dienoate (50.0 mg, 0.210 mmol), $Mg(ClO_4)_2$ (194 mg, 0.420 mmol), I_2 (198 mg, 0.840 mmol), NEt_3 (73 μL, 0.53 mmol), and NaI (126 mg, 0.840 mmol). The crude residue was purified by flash chromatography (10 % EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (39 mg, 0.17 mmol, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.57 (m, 1H, C**H**=CH), 5.55–5.43 (m, 1H, CH=C**H**), 4.14 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH_3), 3.67–3.43 (m, 1H, C**H**), 3.14–2.98 (m, 1H, C**H$_2$**CH=CH), 2.73–2.77 (m, 1H, C**H$_2$**CH=CH), 2.18–2.99 (m, 2H, CH_2C**H$_2$**), 1.66 (t, *J* = 6 Hz, 2H, CC**H$_2$**CH_2), 1.61–1.45 (m, 1H, CH_2C**H$_2$**), 1.22 (t, *J* = 6 Hz, 3H, OCH_2C**H$_3$**), 1.13 (s, 3H, (C**H$_3$**)$_2$), 1.08 (s, 3H, (C**H$_3$**)$_2$); ^{13}C NMR (100 MHz, CDCl3) δ 212.9, 172.2, 133.1, 128.8, 64.0, 61.4, 50.5, 44.6, 41.5, 35.4, 26.9, 26.2, 23.4, 14.0; IR (thin film) 2977, 2933, 2870, 1739.2, 1708, 1459, 1228, 1111, 1091, 1056 cm^{-1}; MS (APCI+) *m/z* = 237.15 calc'd for $C_{14}H_{21}O_3$ [MH]+, found 237.32.

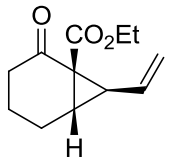


(±)-(3*S*,7*S*)-Ethyl 2-methyl-7-oxo-3,4,5,6,7,7-hexahydro-1H-indene-7-carboxylate: Prepared according to general procedure A from (*E*)-ethyl 9-methyl-3-oxodeca-7,9-dienoate (50.0 mg, 0.223 mmol), $Mg(ClO_4)_2$ (100 mg, 0.446 mmol), I_2 (226 mg, 0.892 mmol), NEt_3 (78 μL, 0.558 mmol), and NaI (0.134 g, 0.892 mmol). The crude residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (23 mg, 0.10 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (br s, 1H, C**H**=C(CH_3)), 4.17 (m, 2H, OC**H$_2$**CH_3), 3.62–3.49 (m, 1H, C**H**), 3.09–2.94 (m, 1H, C**H$_2$**CH=CH), 2.83–2.66 (m, 1H, C**H$_2$**CH=CH), 2.59–2.31 (m, 2H, C**H$_2$**C=O), 2.09–1.61 (m, 7H, C**H$_2$**C**H$_2$** + CH=CC**H$_3$**), 1.25 (t, *J* = 6 Hz, 3H, OCH_2C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 208.7, 172.0, 140.0, 126.0, 65.8, 61.4, 51.7, 43.2, 39.9, 26.9, 21.5, 16.4, 14.1; IR (thin film) 2936, 1711, 1636, 1445, 1231, 1098 cm^{-1}; MS (APCI+) *m/z* = 223.13 calc'd for $C_{13}H_{19}O_3$ [MH]+, found 223.28.



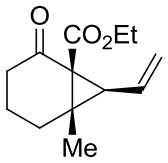
(±)-(3*S*,7*S*)-Ethyl 3-methyl-7-oxo-3,4,5,6,7,7-hexahydro-1H-indene-7-carboxylate: $Mg(ClO_4)_2$ (100 mg, 0.446 mmol) was added to a 25 mL round-bottom flask and purged three times with argon. EtOAc (10 mL) was added followed by the (*E*)-ethyl 8-methyl-3-oxodeca-7,9-dienoate (50.0 mg, 0.223 mmol), iodine (226 mg, 0.892 mmol), and NEt_3

(78 μL, 0.558 mmol). The reaction mixture was allowed to stir at room 85% yitemperature for three hours. Aqueous HCl solution (1.0M, 10 mL) was then added. The aqueous layer was then extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed successively with saturated $Na_2S_2O_3$ solution and brine (20 mL each), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (10 % EtOAc in hexanes) to afford the title cyclopentene as a colorless oil (42 mg, 0.189 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (s, 1H, C**H**=CH), 4.16 (m, 2H, OC**H$_2$**CH$_3$), 3.45–3.27 (m, 1H, C**H**), 3.11–2.94 (m, 1H, C**H$_2$**CH=CH), 2.78–2.61 (m, 1H, C**H$_2$**CH=CH), 2.59–2.30 (m, 2H, C**H$_2$**C=O), 2.13–1.94 (m, 1H, C**H$_2$**CH$_2$), 1.94–1.76 (m, 1H, C**H$_2$**CH$_2$), 1.75–1.51 (m, 5H, C**H$_2$**CH$_2$ + C=CC**H$_3$**),1.23 (t, 3H, *J* = 6 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 208.3, 172.2, 139.5, 124.0, 65.8, 61.4, 53.7, 39.8, 37.7, 24.9, 21.5, 14.3, 14.0; IR (thin film) 2937, 2867, 1737, 1712, 1631, 1444, 1230, 1102, 1031 cm^{-1}; MS (APCI+) *m/z* = 223.13 calc'd for $C_{13}H_{19}O_3$ [MH]+, found 223.29.



(±)-(1*R*,6*S*,7*S*)-Ethyl 2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure B from (*E*)-ethyl 3-oxoundeca-8,10-dienoate (50 mg, 0.24 mmol), $Mg(ClO_4)_2$ (106 mg, 0.47 mmol), I_2 (226 mg, 0.89 mmol), and NEt_3 (83 μL, 0.60 mmol). The crude residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the title vinylcyclopropane as a colorless waxy solid (31 mg, 0.15

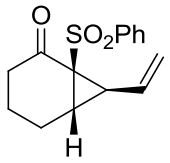
mmol, 63% yield, >20:1 d.r.)[2]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (ddd, 1H, C**H**=CH_2, *J* = 6, 9, 15 Hz), 5.24 (d, 1H, C=C**H$_2$**, *J* = 15 Hz), 5.11 (d, 1H, C=C**H$_2$**, *J* = 9 Hz), 4.19 (q, 2H, OC**H$_2$**CH_3, *J* = 6 Hz), 2.45–2.28 (m, 3H, C**H$_2$**C=O + C**H**$CH=CH_2$), 2.20 (ddd, 1H, C**H**, *J* = 6, 12, 18 Hz), 2.07–1.98 (m, 2H, C**H$_2$**CH_2), 1.87–1.59 (m, 2H, C**H$_2$**CH_2), 1.12 (t, 3H, *J* = 6 Hz, OCH_2C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 201.1, 167.5, 133.3, 118.0, 61.3, 43.7, 37.8, 33.4, 29.8, 20.8, 19.1, 14.2; IR (thin film) 2944, 1717, 1691, 1636, 1368, 1333, 1261, 1196, 1096, 1080, 1057, 992, 915 cm^{-1}; MS (APCI+) *m/z* = 209.12 calc'd for $C_{12}H_{17}O_3$ [MH]+, found 209.26.



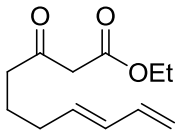
(±)-(1*S*,6*S*,7*S*)-Ethyl 6-methyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate: Prepared according to general procedure B from (*E*)-ethyl 7-methyl-3-oxoundeca-8,10-dienoate (50.0 mg, 0.223 mmol), $Mg(ClO_4)_2$ (100 mg, 0.446 mmol), I_2 (226 mg, 0.892 mmol),, and NEt_3 (78 μL, 0.558 mmol). The crude residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the title vinylcyclopropane as a colorless waxy solid (18 mg, 0.081 mmol, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dt, *J* = 9, 18 Hz, 1H, C**H**=CH_2), 5.27 (d, *J* = 18 Hz, 1H, C=C**H$_2$**), 5.19 (d, *J* = 9 Hz, 1H, C=C**H$_2$**), 4.20 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH_3), 2.46–2.33 (m, 2H, C**H$_2$**C=O + C**H**$CH=CH_2$), 2.26–2.10 (m, 1H, C**H$_2$**C=O), 2.00 (dt, *J* = 6, 15 Hz, 1H, C**H$_2$**CH_2), 1.89 (dd, *J* = 6, 15 Hz, C**H$_2$**CH_2), 1.84–1.65 (m, 2H, C**H$_2$**CH_2), 1.30–1.19 (m, 6H, OCH_2C**H$_3$** + C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 202.9, 167.0, 131.8, 118.1, 61.0, 49.4, 36.2,

[2] Major diastereomer determined by COSY and NOESY.

33.8, 32.0, 29.3, 17.9, 17.6, 14.2; IR (thin film) 2937, 1733, 1690, 1448, 1369, 1327, 1216, 1102, 1076, 912, 750 cm^{-1}; MS (APCI+) *m/z* = 223.13 calc'd for $C_{13}H_{19}O_3$ [MH]+, found 223.29.



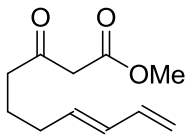
(1R,6S,7S)-1-(Phenylsulfonyl)-7-vinylbicyclo[4.1.0]heptan-2-one: Prepared according to general procedure B from (*E*)-1-(phenylsulfonyl)nona-6,8-dien-2-one (50.0 mg, 0.180 mmol), $Mg(ClO_4)_2$ (80.0 mg, 0.360 mmol), I_2 (183 mg, 0.720 mmol),, and NEt_3 (63 μL, 0.450 mmol). The crude residue was purified by flash chromatography (35% EtOAc in hexanes) to afford the title vinylcyclopropane as a colorless waxy solid (18 mg, 0.065 mmol, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9 Hz, 2H, $C_6\mathbf{H_5}$), 7.58 (t, *J* = 9 Hz, 1H, $C_6\mathbf{H_5}$), 7.50 (t, *J* = 9 Hz, 2H, $C_6\mathbf{H_5}$), 6.17 (dt, *J* = 9, 15 Hz, 1H, C**H**=CH_2), 5.38–5.19 (m, 2H, C=C$\mathbf{H_2}$), 3.05–2.91(m, 1H, C**H**CH=CH_2**),** 2.49–2.22 (m, 2H, C$\mathbf{H_2}$C=O), 2.21–1.98 (m, 3H, CH + C$\mathbf{H_2}$$CH_2$), 1.87–1.49 (m, 2H, CH_2C$\mathbf{H_2}$); ^{13}C NMR (100 MHz, CDCl3) δ 198.7, 140.5, 133.4, 131.6, 129.2, 128.4, 120.3, 56.6, 38.5, 34.4, 28.7, 20.8, 18.5; IR (thin film) 2949, 1702, 1447, 1306, 1150, 1082, 995, 920, 830, 758, 722, 688 cm^{-1}; MS (APCI+) *m/z* = 277.09 calc'd for $C_{15}H_{17}O_3S$ [MH]+, found 277.28.



(*E*)-Ethyl 3-oxodeca-7,9-dienoate: Ethyl acetoacetate (3.81mL, 29.9 mmol) was added to THF (190 mLs) and cooled to -10 °C (salt/ice bath). Sodium hydride (60% in mineral oil, 1.10g, 27.6 mmol) was then added in three portions over five minutes with rapid stirring. The reaction was then stirred for 15 minutes at -10 °C. A solution of butyl lithium (2.5M in hexanes, 11.0 mL, 27.6 mmol) was then added over 10 minutes to the reaction mixture. The reaction was allowed to stir for 10 minutes at -10 °C. A solution of (*E*)-6-iodohexa-1,3-diene[3] (4.78g, 23.0 mmol) in THF (30 mL) was then added rapidly. The reaction mixture was allowed to warm to room temperature and stirred for three hours. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (150 mL). The mixture was then extracted three times with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title compound (2.20g, 10.5 mmol, 46% yield, 9:1 keto/enol by NMR in $CDCl_3$) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.08 (s, 1H, O**H** enol), 6.27 (dt, *J* = 9, 18 Hz, 1H, CH=CHC**H**=CH_2), 6.03 (dd, *J* = 12, 18 Hz, 1H, CH=C**H**CH=CH_2), 5.62 (dt, *J* = 6, 12 Hz, 1H, C**H**=CHCH=CH_2), 5.07 (d, *J* = 18 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 4.95 (d, *J* = 12 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 4.16 (q, *J* = 6 Hz, 2H, OC$\mathbf{H_2}$$CH_3$), 3.39 (s, 1H, C=OC$\mathbf{H_2}$C=O), 2.52 (t, *J* = 9 Hz, 2H, C$\mathbf{H_2}$C=O) , 2.08 (q, *J* = 6 Hz, 2H, C**H**CH=CH), 1.69 (q, *J* = 6 Hz, 2H, CH_2C$\mathbf{H_2}$$CH_2$), 1.25 (t, *J* = 6 Hz, 3H, OCH_2C$\mathbf{H_3}$); ^{13}C NMR (100 MHz, CDCl3) δ 202.5, 167.1, 136.9, 133.7, 131.8, 61.2, 49.3, 42.1, 31.5, 22.7, 14.0; IR

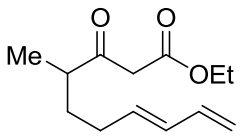
[3] Brodney, M.; O'Leary, J.; Hansen, J.; Giguere, R. *Synth. Commun.* **1995**, *25*, 521 – 532.

(thin film) 2945, 1702, 1447, 1306, 1150, 1082, 995, 920, 830, 758, 722, 688 cm^{-1}; MS (APCI+) *m/z* = 211.13 calc'd for $C_{12}H_{19}O_3$ [MH]+, found 211.28.



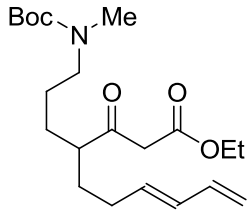
(*E*)-Methyl 3-oxodeca-7,9-dienoate: Methyl acetoacetate (2.02 mL, 18.7 mmol) was added to THF (100 mLs) and cooled to -10 °C (salt/ice bath). Sodium hydride (60% in mineral oil, 0.692g, 17.3 mmol) was then added in three portions over five minutes with rapid stirring. The reaction was then stirred for 15 minutes at -10 °C. A solution of butyl lithium (2.5M in hexanes, 6.92 mL, 17.3 mmol) was then added over 10 minutes to the reaction mixture. The reaction was allowed to stir for 10 minutes at -10 °C. A solution of (*E*)-6-iodohexa-1,3-diene (3.0 g, 14.4 mmol) in THF (15 mL) was then added rapidly. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (100 mL). The mixture was then extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title compound (1.22 g, 6.22 mmol, 43% yield, 12:1 keto/enol by NMR in $CDCl_3$) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.98 (s, 1H, O**H** enol), 6.25 (dt, *J* = 12, 18 Hz, 1H, CH=CHC**H**=CH_2), 6.00 (dd, *J* = 12, 18 Hz, 1H, CH=C**H**CH=CH_2), 5.59 (dt, *J* = 9, 12 Hz, 1H, C**H**=CHCH=CH_2), 5.05 (d, *J* = 18 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 4.93 (d, *J* = 12 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 3.68 (s, 3H, OC$\mathbf{H_3}$), 3.39 (s, 1H, C=OC$\mathbf{H_2}$C=O), 2.50 (t, *J* = 6 Hz, 2H, C$\mathbf{H_2}$C=O) , 2.06 (q, *J* = 6 Hz, 2H, C**H**CH=CH), 1.67 (q, *J* = 6 Hz, 2H,

$CH_2C\mathbf{H_2}CH_2$); ^{13}C NMR (100 MHz, CDCl3) δ 202.2, 167.4, 136.8, 133.6, 131.8, 115.2, 52.1, 48.9, 42.0, 31.4, 22.6; IR (thin film) 2952, 1748, 1716, 1651, 1438, 1408, 1321, 1257, 1159, 1093, 1006, 901 cm^{-1}; MS (APCI+) *m/z* = 197.12 calc'd for $C_{11}H_{17}O_3$ [MH]+, found 197.24.



(±)-(*E*)-Ethyl 4-methyl-3-oxodeca-7,9-dienoate: To a stirred suspension of NaH (60% in mineral oil, 0.278 g, 6.94 mmol) in THF (25 mL) at 0 °C was added ethyl 3-oxovalerate (1.00 g, 6.94 mmol) dropwise over five minutes. The reaction mixture was then allowed to stir at this temperature for 15 minutes and was then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 2.78 mL, 6.94 mmol) was added dropwise over ten minutes. The reaction mixture was allowed to warm to 0 °C and (*E*)-6-iodohexa-1,3-diene (1.20 g, 5.78 mmol) in THF (5 mL) was added. The reaction mixture was then stirred overnight, allowing the flask to warm to room temperature. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (25 mL). The mixture was then extracted three times with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title compound (0.453 g, 2.02 mmol, 35% yield, 7:1 keto/enol by NMR in $CDCl_3$) as a colorless oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 12.11 (s, 1H, O**H** enol) 6.28 (dt, *J* = 9, 18 Hz, 1H, CH=CHC**H**=CH_2), 6.04 (dd, *J* = 12, 18 Hz, 1H, CH=C**H**CH=CH_2), 5.71–5.54 (m, 1H, C**H**=CHCH=CH_2), 5.09 (d, *J* = 18 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 4.96 (d, *J* = 12 Hz, 1H,

CH=CHCH=C**H$_2$**), 4.95 (s, 1H, O**H** enol), 4.17 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH$_3$), 3.45 (s, 2H, C=OC**H$_2$**C=O), 2.64 (sex, *J* = 9 Hz, 1H, C**H**C=O) , 2.07 (q, *J* = 6 Hz, 2H, C**H**CH=CH), 1.89–1.71 (m, 1H, CHC**H$_2$**CH$_2$), 1.53–1.34 (m, 1H, CHC**H$_2$**CH$_2$), 1.25 (t, *J* = 6 Hz, 3H, OCH$_2$C**H$_3$**), 1.11 (d, J = 6 Hz, 1H, C**H$_3$**CH); ^{13}C NMR (100 MHz, CDCl3) δ 206.1, 167.2, 137.1 (enol), 136.9, 134.2 (enol), 133.7, 131.8, 131.4 (enol), 115.3, 115.0 (enol), 88.2 (enol), 61.2, 59.9 (enol), 47.7, 45.8, 38.9 (enol), 33.3 (enol), 31.8, 30.0 (enol), 29.9, 17.9 (enol), 15.9, 14.1; IR (thin film) 2976, 2935, 1745, 1713, 1648, 1627, 1368, 1309, 1232, 1152, 1112, 1028, 1007, 890 cm^{-1}; MS (APCI+) *m/z* = 225.15 calc'd for $C_{13}H_{21}O_3$ [MH]+, found 225.27.



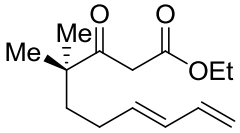
(±)-(*E*)-Ethyl 4-(N-*BOC*-N-methyl-3-propyl)-3-oxodeca-7,9-dienoate: A solution of ethyl acetoacetate (0.652 mL, 5.12 mmol) in THF (25 mL) was cooled to -10 °C (salt/ice bath). NaH (60% in mineral oil, 0.189 g, 4.73 mmol) was added in two portions over ten minutes. The reaction mixture was allowed to stir for fifteen minutes at this temperature. Butyl lithium (2.5M in hexanes, 1.89 mL, 4.73 mmol) was then added dropwise at -10 °C over ten minutes. The reaction mixture was allowed to stir for ten additional minutes at the same temperature and then tert-butyl 3-iodopropyl(methyl)carbamate[4] (1.18 g, 3.94 mmol) in THF (5 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched by addition of a solution of

[4] AstraZeneca AB; *Adamantane Derivatives*. US 6,242,470 B1, **2001**.

saturated aqueous NH_4Cl (25 mL). The mixture was then extracted with ether (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (20% EtOAc in hexanes) to yield ethyl 7-(tert-butoxycarbonyl(methyl)amino)-3-oxoheptanoate (0.480 g, 1.59 mmol, 34% yield) as a colorless oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 4.20 (q, J = 6 Hz, 2H, OC**H$_2$**CH_3), 3.42 (s, 1H, C=OC**H$_2$**C=O), 3.27–3.14 (m, 2H, NC**H$_2$**CH_2), 2.82 (s, 3H, C**H$_3$**N), 2.58 (t, J = 6 Hz, 2H, C**H$_2$**C=O), 1.66–1.47 (m, 4H, C**H$_2$**C**H$_2$**), 1.45 (s, 9H, C(C**H$_3$**)$_3$), 1.28 (t, J = 6 Hz, 3H, OCH_2C**H$_3$**).

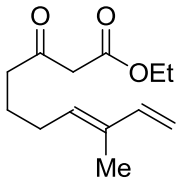
A solution of ethyl 7-(tert-butoxycarbonyl(methyl)amino)-3-oxoheptanoate (0.460 mL, 1.53 mmol) in THF (10 mL) was cooled to -10 °C (salt/ice bath). NaH (60% in mineral oil, 0.061 g, 1.5 mmol) was added. The reaction mixture was allowed to stir for fifteen minutes at this temperature. Butyl lithium (2.5M in hexanes, 0.61 mL, 1.5 mmol) was then added dropwise at -10 °C over ten minutes. The reaction mixture was allowed to stir for ten additional minutes at the same temperature and then (*E*)-6-iodohexa-1,3-diene (0.318 g, 1.53 mmol) in THF (2 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (10 mL). The mixture was then extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (20% EtOAc in hexanes) to yield the title compound (0.221 g, 0.58 mmol, 38% yield) as a colorless oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 6.27 (dt, J = 9, 18 Hz, 1H, CH=CHC**H**=CH_2), 6.10–5.95 (m, 1H, CH=C**H**CH=CH_2), 5.72–5.54 (m, 1H, C**H**=CHCH=CH_2), 5.09 (d, J = 18 Hz, 1H, CH=CHCH=C**H$_2$**), 4.96 (s, 1H, C=C**H** enol),

4.96 (d, *J* = 12 Hz, 1H, CH=CHCH=C**H$_2$**), 4.17 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH$_3$), 3.49 (s, 2H, C=OC**H$_2$**C=O),3.23–3.10 (m, 2H, NC**H$_2$**), 2.80(s, 3H, NC**H$_3$**), 2.69–2.52 (m, 1H, C**H**C=O), 2.12–1.96 (m, 2H, C**H$_2$**CH=CH), 1.83–1.32 (m, 6H, C**H$_2$**CH$_2$), 1.43(s, 9H, C(C**H$_3$**)$_3$), 1.26 (t, *J* = 6 Hz, 3H, OCH$_2$C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 206.1, 173.0 (enol), 167.4, 156.2, 137.5, 134.1, 132.5, 115.6, 90.5, 79.7, 61.7, 60.4, 51.7, 48.9, 45.3, 34.4, 32.6, 30.8, 30.6, 30.4, 30.1, 28.8, 28.3, 14.6, 14.5; IR (thin film) 2975, 2933, 1744, 1693, 1454, 1395, 1366, 1309, 1233, 1161, 1032 cm^{-1}; MS (APCI+) *m/z* = 382.26 calc'd for $C_{21}H_{36}NO_5$ [MH]+, found 237.1487.



(*E*)-Ethyl 4,4-dimethyl-3-oxodeca-7,9-dienoate: To a stirred suspension of NaH (60% in mineral oil, 0.692 g, 17.3 mmol) in THF (60 mL) at 0 °C was added ethyl 4-methyl-3-oxovalerate (2.73 g, 17.3 mmol) in THF (5 mL) dropwise over five minutes. The reaction mixture was then allowed to stir at this temperature for 15 minutes and was then cooled to -78 °C. Butyl lithium (2.5M in hexanes, 6.92 mL, 17.3 mmol) was added dropwise over ten minutes. The reaction mixture was allowed to warm to 0 °C and (*E*)-6-iodohexa-1,3-diene (3.00 g, 14.4 mmol) in THF (10 mL) was added. The reaction mixture was then stirred overnight, allowing the flask to warm to room temperature. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (60 mL). The mixture was then extracted three times with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title

compound (0.754 g, 3.17 mmol, 22% yield, 3:1 keto/enol by NMR in $CDCl_3$) as a light yellow oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 6.27 (dt, *J* = 9, 18 Hz, 1H, CH=CHC**H**=CH_2), 6.10–5.95 (m, 1H, CH=C**H**CH=CH_2), 5.72–5.57 (m, 1H, C**H**=CHCH=CH_2), 5.08 (d, *J* = 18 Hz, 1H, CH=CHCH=C**H$_2$**), 5.01 (s, 1H, C=C**H** enol), 4.96 (d, *J* = 12 Hz, 1H, CH=CHCH=C**H$_2$**), 4.18 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH_3), 3.49 (s, 1H, C=OC**H$_2$**C=O), 2.05–1.91 (m, 2H, C**H$_2$**CH=CH) , 1.67–1.53 (m, 2H, C**H$_2$**CH_2), 1.27 (t, *J* = 6 Hz, 3H, OCH_2C**H$_3$**), 1.15 (s, 1H, (C**H$_3$**)$_2$ keto), 1.12 (s, 1H, (C**H$_3$**)$_2$ enol); ^{13}C NMR (100 MHz, CDCl3) δ 207.5, 167.6, 137.2 (enol), 137.0, 134.9 (enol), 134.1, 131.3, 130.9 (enol), 115.3, 114.8 (enol), 87.1, 61.2, 59.9 (enol), 48.0, 44.2, 39.7 (enol), 39.0, 27.8 (enol), 27.6, 25.4, 23.9, 14.2 (enol), 14.1; IR (thin film) 2973, 2937, 1746, 1707, 1648, 1618, 1469, 1414, 1367, 1305, 1267, 1213, 1144, 1096, 1035, 1006, 899 cm^{-1}; MS (APCI+) *m/z* = 239.17 calc'd for $C_{14}H_{23}O_3$ [MH]+, found 239.29.



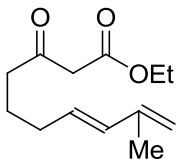
(*E*)-Ethyl 8-methyl-3-oxodeca-7,9-dienoate: To CH_2Cl_2 (75 mL) was added triphenylphosphine (6.43 g, 24.5 mmol), imidazole (1.67 g, 24.5 mmol), and iodine (6.22 g, 24.5 mmol). (*E*)-4-Methylhexa-3,5-dien-1-ol[5] (2.02 g, 18.0 mmol) was added. Reaction was stirred for 15 min then diluted with pentane (50 mL) then filtered through 2" of silica, eluting with pentane. The collected solution was then concentrated *in vacuo*

[5] Kim, P.; Nantz, M.; Kurth, M.; Olmstead, M. *Org. Lett.* **2000**, *2*, 1831-1834.

to yield the corresponding iodide that was used immediately in the following procedure without further purification.

A solution of ethyl acetoacetate (1.90 mL, 15.0 mmol) in THF (100 mL) was cooled to -10 °C (salt/ice bath). NaH (60% in mineral oil, 0.552 g, 13.8 mmol) was added in three portions over ten minutes. The reaction mixture was allowed to stir for fifteen minutes at this temperature. Butyl lithium (2.5M in hexanes, 5.52 mL, 13.8 mmol) was then added dropwise at -10 °C over ten minutes. The reaction mixture was allowed to stir for ten additional minutes at the same temperature and then (E)-6-iodo-3-methylhexa-1,3-diene (2.55g, 11.5 mmol) in THF (15 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (100 mL). The mixture was then extracted with ether (3 × 75 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title compound (0.970 g, 4.33 mmol, 38% yield, 12:1 keto/enol by NMR in $CDCl_3$) as a colorless oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 12.08 (s, 1H, O**H** enol), 6.33 (dd, *J* = 12, 18 Hz, 1H, CH=C(CH_3)C**H**=CH_2), 5.41 (t, *J* = 9 Hz, 1H, C**H**=C(CH_3)), 5.06 (d, *J* = 18 Hz, 1H, CH=C**H$_2$**), 4.90 (d, *J* = 12 Hz, 1H, C(CH_3)=C**H$_2$**), 4.16 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH_3), 3.38 (s, 1H, C=OC**H$_2$**C=O), 2.52 (t, *J* = 6 Hz, 2H, C**H$_2$**C=O), 2.13 (q, *J* = 6 Hz, 2H, C**H**CH=CH), 1.75–1.59 (m, 5H, C(C**H$_3$**)=CH + CH_2C**H$_2$**CH_2), 1.24 (t, *J* = 6 Hz, 3H, OCH_2C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 202.5, 167.1, 141.2, 134.9, 131.6, 110.8, 61.2, 49.2, 42.2, 27.2, 23.1, 14.0, 11.6; IR (thin film) 2981, 2938, 1744, 1716, 1643,

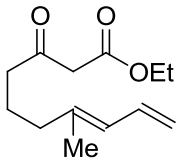
1412, 1368, 1315, 1238, 1176, 1094, 1303, 896 cm^{-1}; MS (APCI+) *m/z* = 225.15 calc'd for $C_{13}H_{21}O_3$ [MH]+, found 225.27.



(*E*)-Ethyl 9-methyl-3-oxodeca-7,9-dienoate: A solution of ethyl acetoacetate (1.92 mL, 15.1 mmol) in THF (90 mL) was cooled to -10 °C (salt/ice bath). NaH (60% in mineral oil, 0.556 g, 13.9 mmol) was added in three portions over ten minutes. The reaction mixture was allowed to stir for fifteen minutes at this temperature. Butyl lithium (2.5M in hexanes, 5.56 mL, 13.9 mmol) was then added dropwise at -10 °C over ten minutes. The reaction mixture was allowed to stir for ten additional minutes at the same temperature and then (E)-6-iodo-2-methylhexa-1,3-diene[6] (2.58g, 11.6 mmol) in THF (15 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (90 mL). The mixture was then extracted with ether (3 × 60 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title compound (1.25 g, 5.57 mmol, 48% yield, 9:1 keto/enol by NMR in $CDCl_3$) as a colorless oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 12.08 (s, 1H, O**H** enol), 6.11 (d, *J* = 15 Hz, 1H, CH=C**H**C(CH_3)=CH_2), 5.56 (dt, *J* = 9, 15 Hz, 1H, C**H**=CHC(CH_3)=CH_2), 4.95 (s, 1H, C=C**H**C=O enol), 4.85 (s, 2H, C(CH_3)=C$\mathbf{H_2}$), 4.16 (q, *J* = 6 Hz, 2H, OC$\mathbf{H_2}$$CH_3$), 3.39 (s, 1H, C=OC$\mathbf{H_2}$C=O), 2.52 (t, *J* = 6 Hz, 2H, C$\mathbf{H_2}$C=O), 2.10 (q, *J* = 6 Hz, 2H,

[6] Coscia, R.; Lambert, T. *J. Amer. Chem. Soc.* **2009**, *131*, 2496 – 2498.

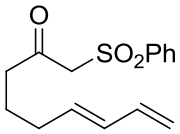
C**H**CH=CH), 1.79 (s, 3H, C(C**H$_3$**)=CH$_2$**),** 1.70 (p, *J* = 6 Hz, 2H, CH$_2$C**H$_2$**CH$_2$), 1.25 (t, *J* = 6 Hz, 3H, OCH$_2$C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 202.5, 167.1, 141.8, 133.8, 129.3, 114.6, 61.2, 49.3, 42.1, 31.8, 22.9, 18.5, 14.0; IR (thin film) 2981, 2939, 1744, 1716, 1645, 1442, 1411, 1369, 1314, 1238, 1097, 1031, 968, 885 cm^{-1}; MS (APCI+) *m/z* = 225.15 calc'd for $C_{13}H_{21}O_3$ [MH]+, found 225.27.



(*Z*)-Ethyl 7-methyl-3-oxodeca-7,9-dienoate: A solution of ethyl acetoacetate (1.02 mL, 8.00 mmol) in THF (50 mL) was cooled to -10 °C (salt/ice bath). NaH (60% in mineral oil, 0.295 g, 7.38 mmol) was added in three portions over ten minutes. The reaction mixture was allowed to stir for fifteen minutes at this temperature. Butyl lithium (2.5M in hexanes, 2.95 mL, 7.38 mmol) was then added dropwise at -10 °C over ten minutes. The reaction mixture was allowed to stir for ten additional minutes at the same temperature and then (E)-6-iodo-4-methylhexa-1,3-diene[7] (1.37g, 6.15 mmol) in THF (10 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (50 mL). The mixture was then extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (5% EtOAc in hexanes) to yield the title compound (0.648 g, 2.89 mmol, 47%

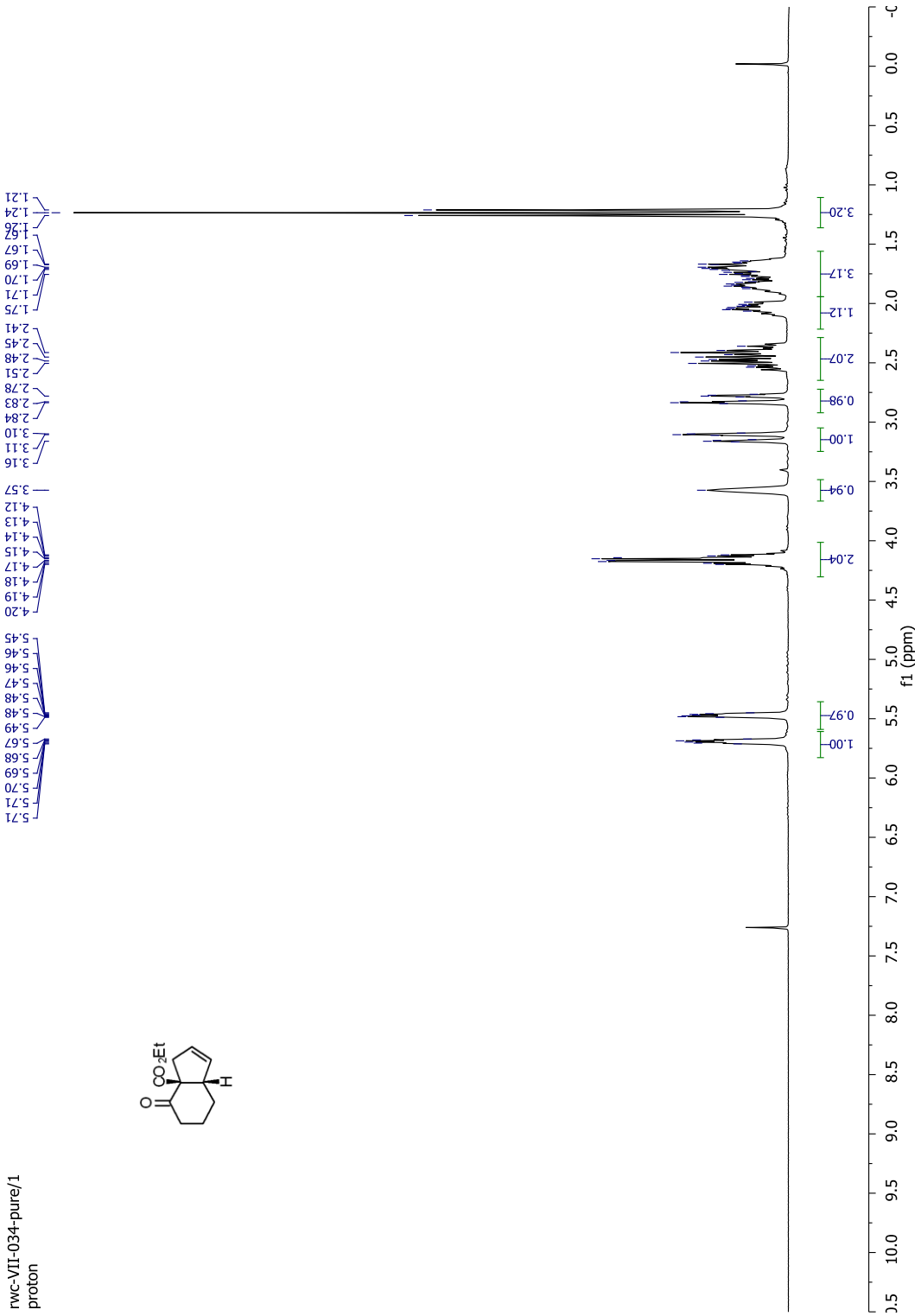
[7] Li, C.; Wang, C.; Liang, B.; Zhang, X.; Deng, L.; Liang, S.; Chen, J.; Wu, Y.; Yang, Z. *J. Org. Chem.* **2006**, *71*, 6892 – 6897.

yield, 14:1 keto/enol by NMR in $CDCl_3$) as a colorless oil. ^{1}HMNR (300 MHz, $CDCl_3$) δ 12.09 (s, 1H, O**H** enol), 6.54 (dt, *J* = 12, 18 Hz, 1H, C(CH_3)=CHC**H**=CH_2), 5.81 (d, *J* = 12 Hz, 1H, C(CH_3)=C**H**CH=CH_2), 4.95 (s, 1H, C=C**H**C=O enol), 5.07 (d, *J* = 18 Hz, 1H, CH=C**H$_2$**), 4.98 (d, *J* = 12 Hz, 1H, CH=C**H$_2$**), 4.17 (q, *J* = 6 Hz, 2H, OC**H$_2$**CH_3), 3.40 (s, 1H, C=OC**H$_2$**C=O), 2.49 (t, *J* = 6 Hz, 2H, C**H$_2$**C=O), 2.05 (t, *J* = 6 Hz, 2H, C**H**(CH_3)=CH), 1.82–1.61 (m, 5H, C(C**H$_3$**)=CH_2 + CH_2C**H$_2$**CH_2), 1.26 (t, *J* = 6 Hz, 3H, OCH_2C**H$_3$**); ^{13}C NMR (100 MHz, CDCl3) δ 202.5, 167.1, 138.2, 133.1, 126.2, 115.0, 61.2, 49.3, 42.1, 38.7, 21.2, 16.3, 14.0; IR (thin film) 2938, 1744, 1717, 1648, 1414, 1368, 1315, 1239, 1179, 1096, 1029, 901 cm^{-1}; MS (APCI+) *m/z* = 225.15 calc'd for $C_{13}H_{21}O_3$ [MH]+, found 225.25.



(*E*)-1-(phenylsulfonyl)nona-6,8-dien-2-one: A solution of 1-(phenylsulfonyl)propan-2-one (1.77 g, 8.93 mmol) in THF (50 mL) was cooled to -10 °C (salt/ice bath). NaH (60% in mineral oil, 0.330 g, 8.25 mmol) was added in three portions over ten minutes. The reaction mixture was allowed to stir for fifteen minutes at this temperature. Butyl lithium (2.5M in hexanes, 3.30 mL, 8.25 mmol) was then added dropwise at -10 °C over ten minutes. The reaction mixture was allowed to stir for ten additional minutes at the same temperature and then (*E*)-6-iodohexa-1,3-diene (1.42 g, 6.87 mmol) in THF (5 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched by addition of a solution of saturated aqueous NH_4Cl (50 mL). The mixture was then extracted with ether (3 × 50 mL). The combined organic

layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified on silica (10% EtOAc in hexanes) to yield the title compound (0.323 g, 1.16 mmol, 17% yield) as a waxy solid. ^{1}HMNR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9 Hz, 2H, $C_6\mathbf{H_5}$), 7.68 (t, *J* = 9 Hz, 1H, $C_6\mathbf{H_5}$), 7.58 (t, *J* = 9 Hz, 2H, $C_6\mathbf{H_5}$), 6.29 (dt, *J* = 9, 18 Hz, 1H, CH=CHC**H**=CH_2), 6.04 (dd, *J* = 6, 18 Hz, 1H, CH=C**H**CH=CH_2), 5.62 (dt, *J* = 6, 18 Hz, 1H, C**H**=CHCH=CH_2), 5.11 (d, *J* = 18 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 4.99 (d, *J* = 9 Hz, 1H, CH=CHCH=C$\mathbf{H_2}$), 4.14 (s, 1H, C=OC$\mathbf{H_2}$SO2Ph), 2.70 (t, *J* = 6 Hz, 2H, C$\mathbf{H_2}$C=O), 2.08 (q, *J* = 6 Hz, 2H, C**H**CH=CH), 1.68 (p, *J* = 6 Hz, 2H, $CH_2C\mathbf{H_2}CH_2$); ^{13}C NMR (100 MHz, CDCl3) δ 197.9, 138.8, 136.9, 134.3, 133.5, 132.0, 129.3, 128.3, 115.5, 66.9, 43.6, 31.4, 22.5; IR (thin film) 2933, 1719, 1649, 1447, 1321, 1152, 1084, 1008, 899, 737, 688 cm^{-1}; MS (APCI+) *m/z* = 279.11 calc'd for $C_{15}H_{19}O_3S$ [MH]+, found 279.30.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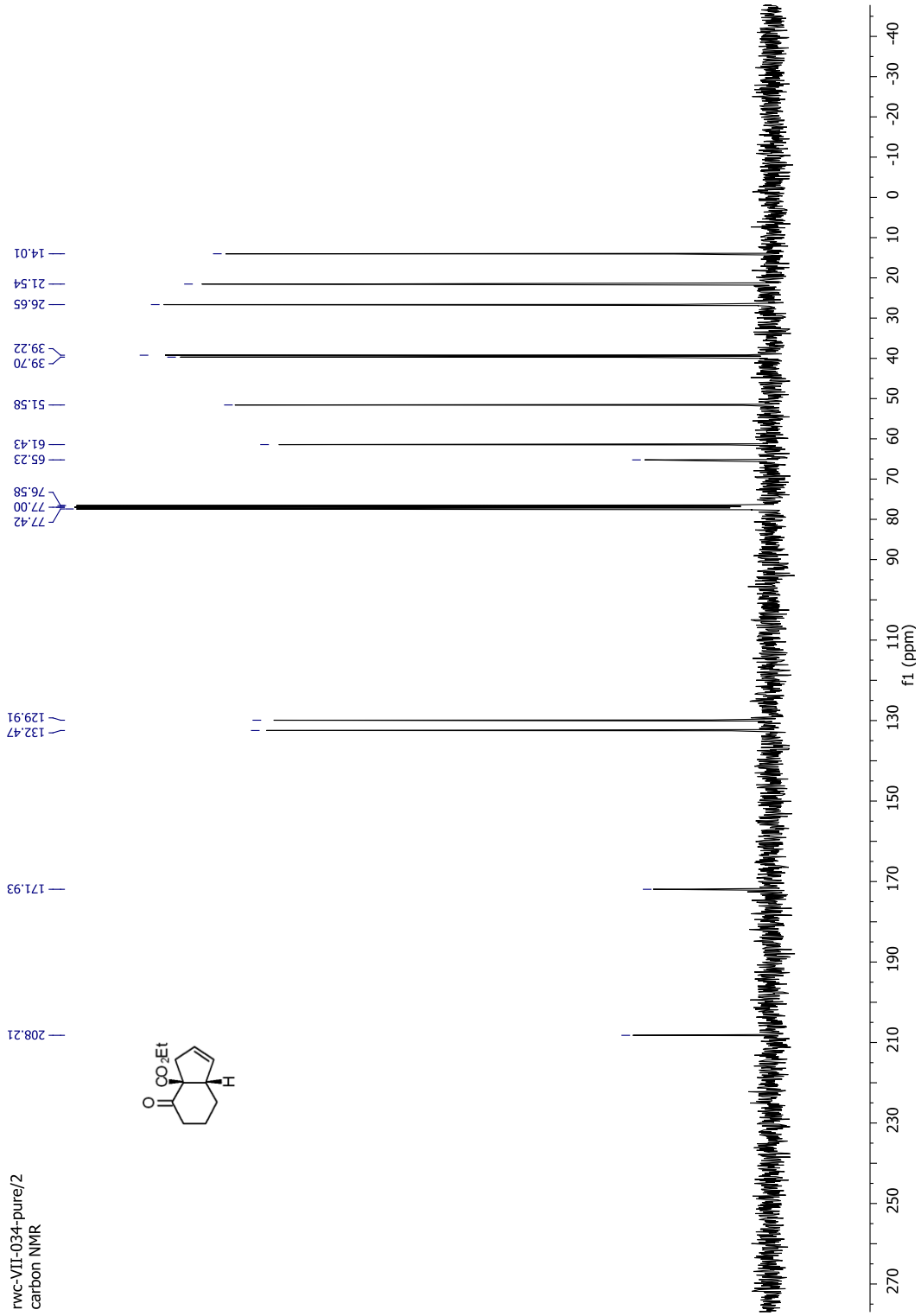
CO2Et
H
O
f1 (ppm)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132.47
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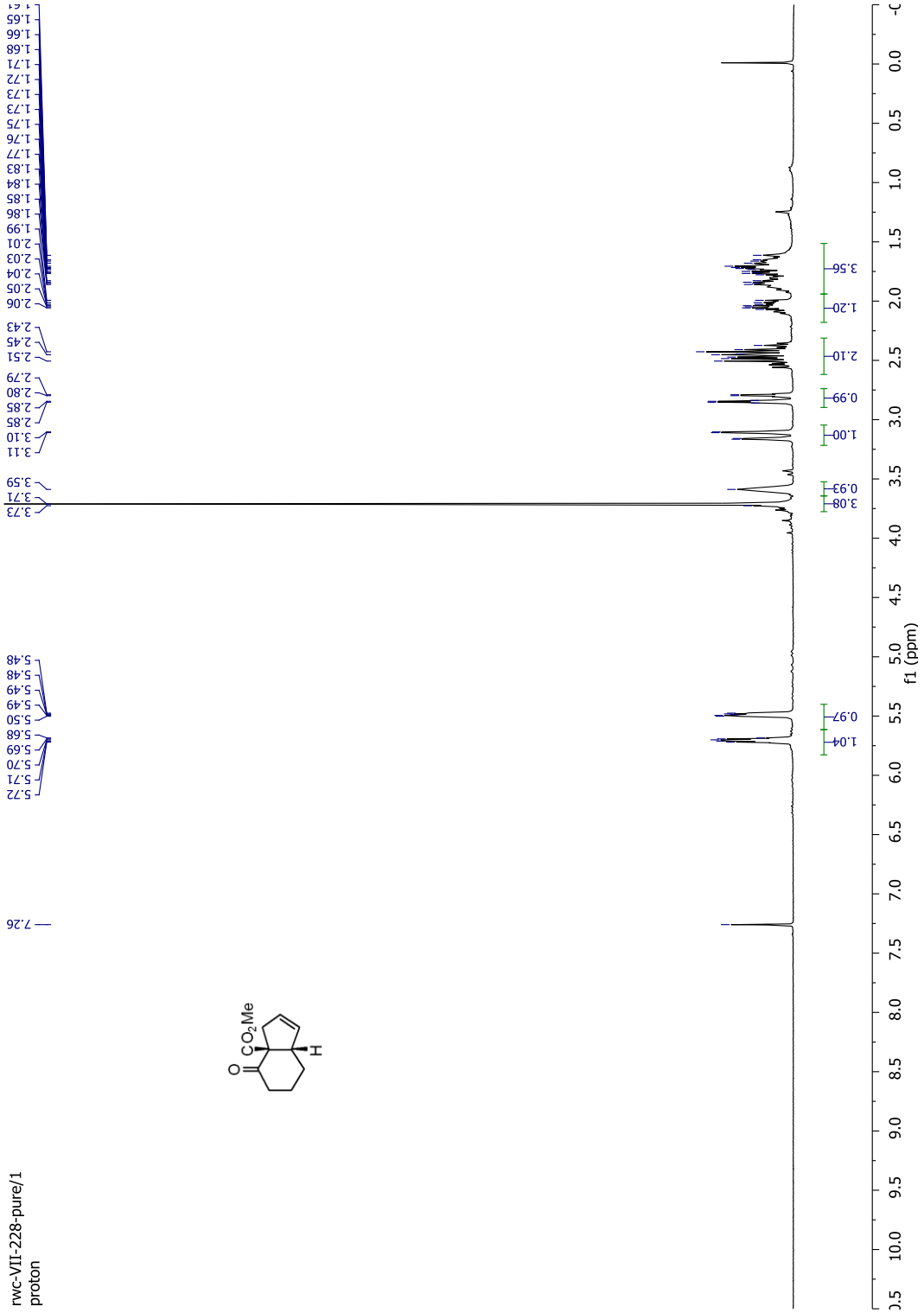
f1 (ppm)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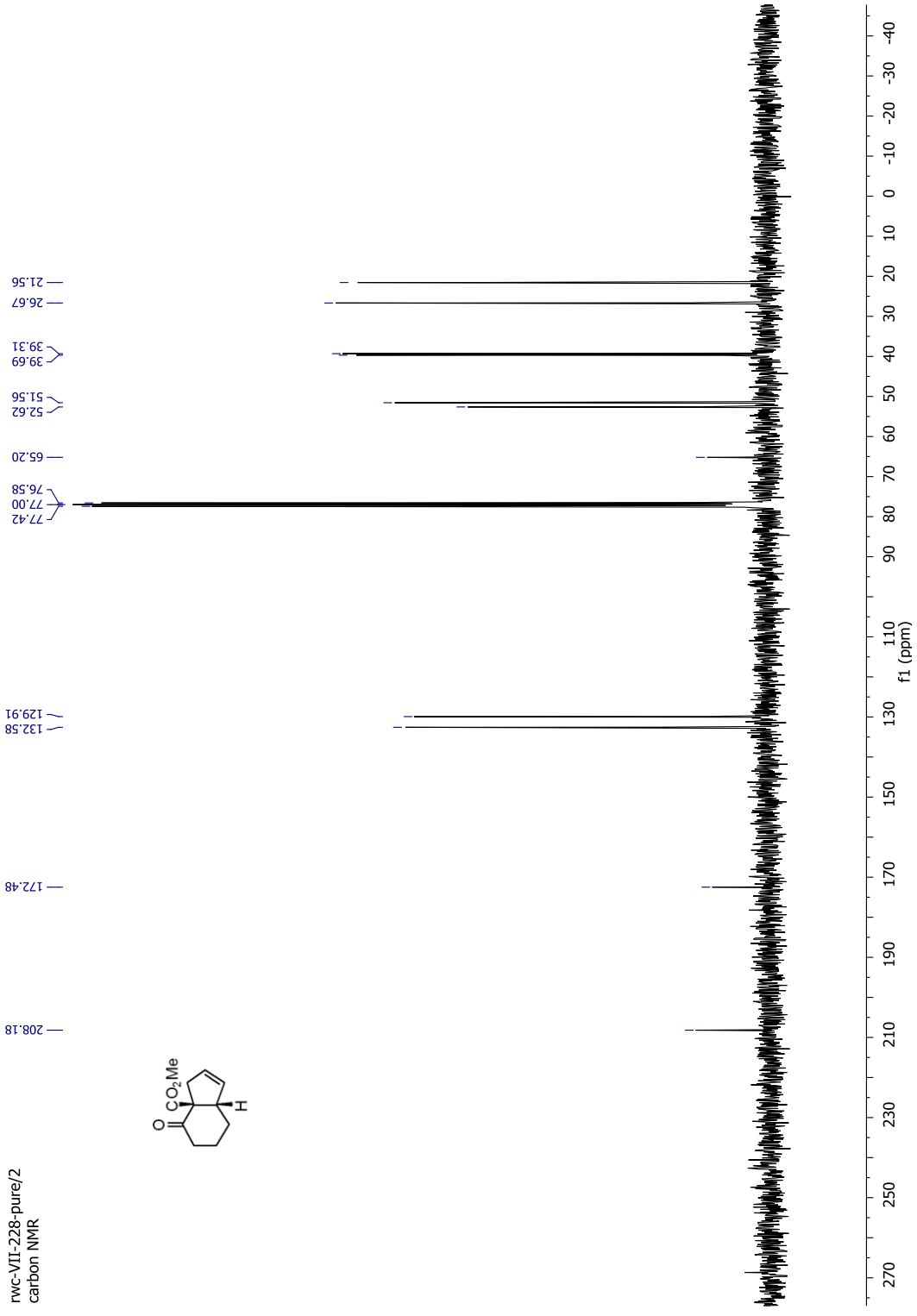
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H
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21.56
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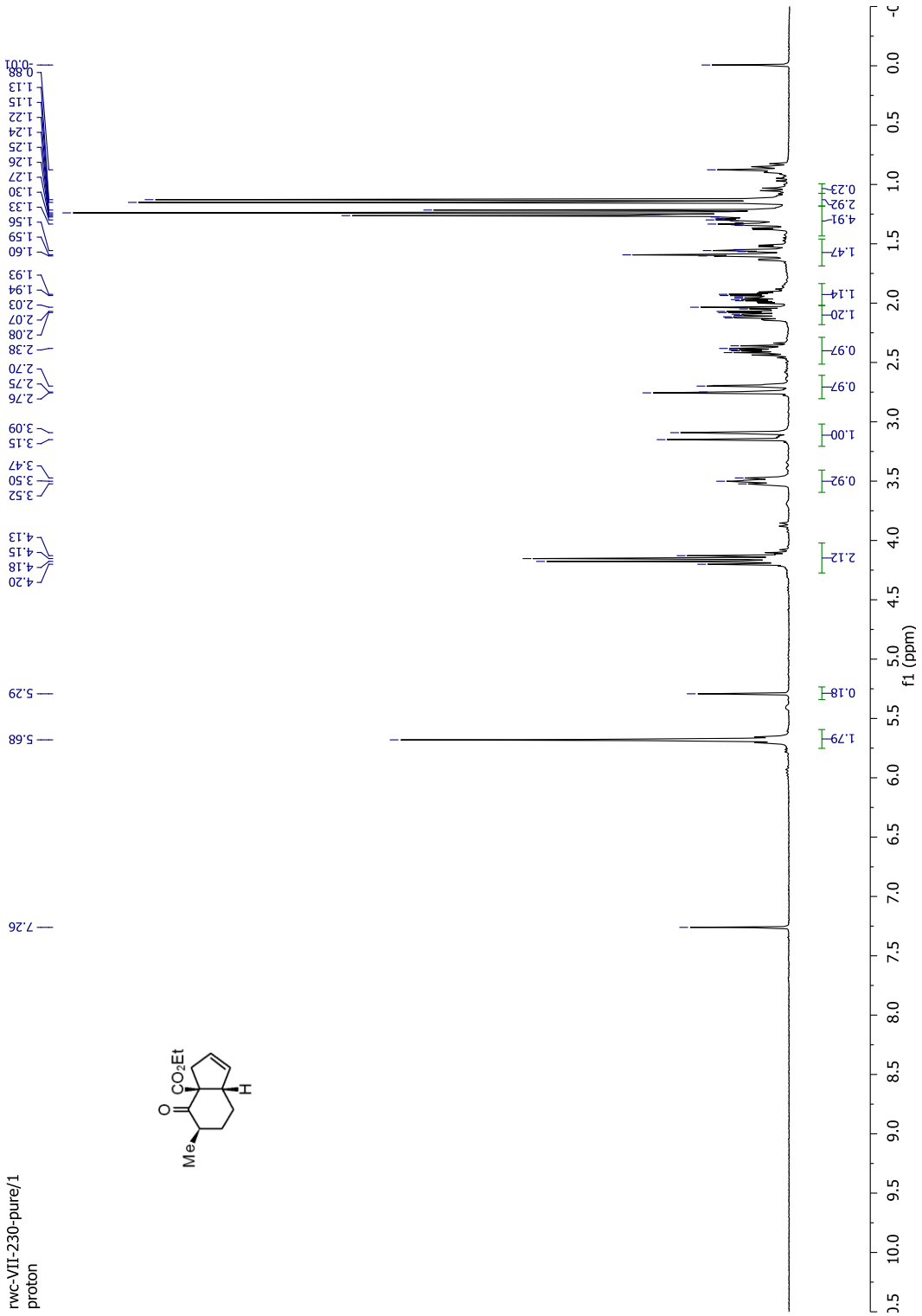
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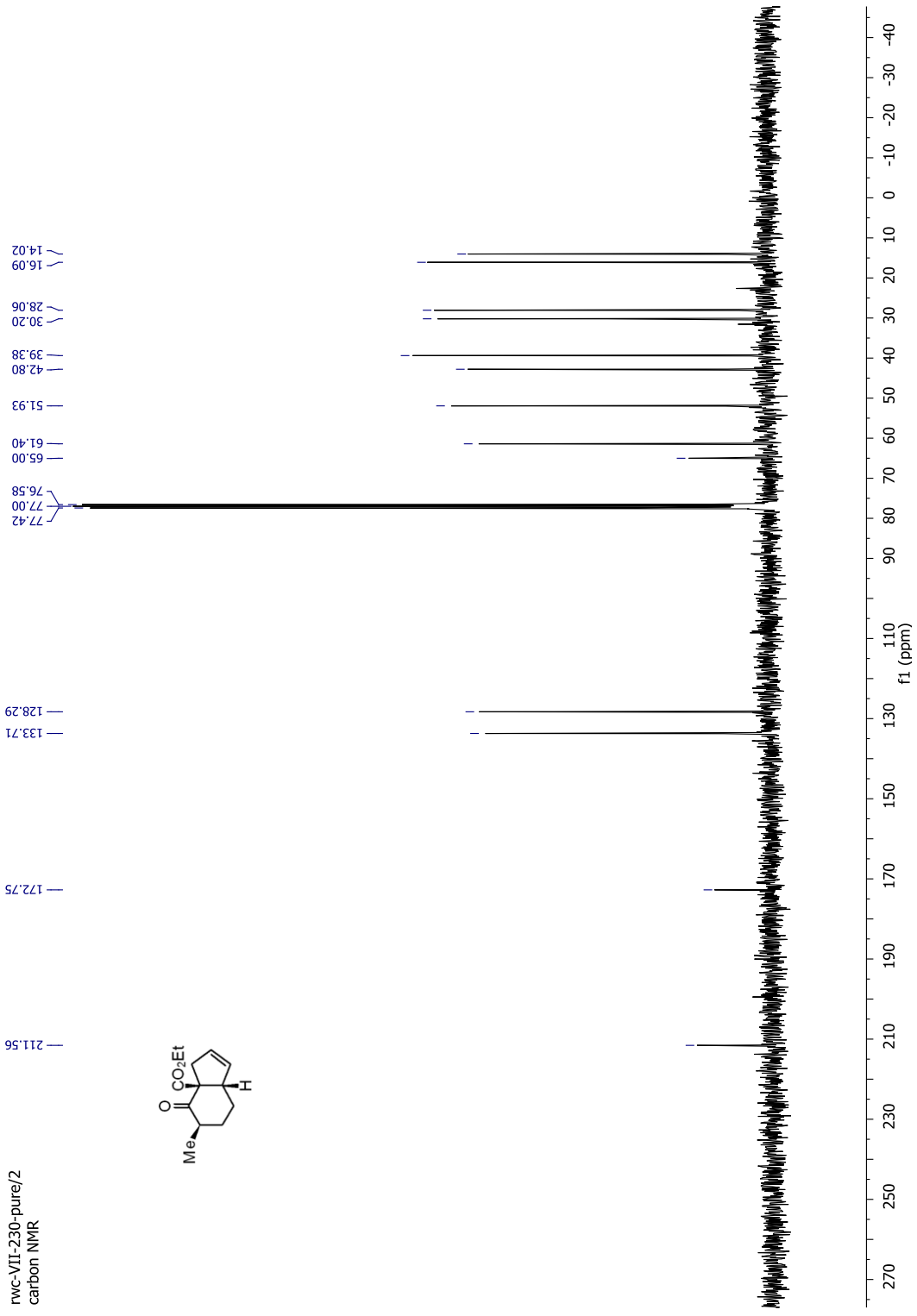
H
Me
f1 (ppm)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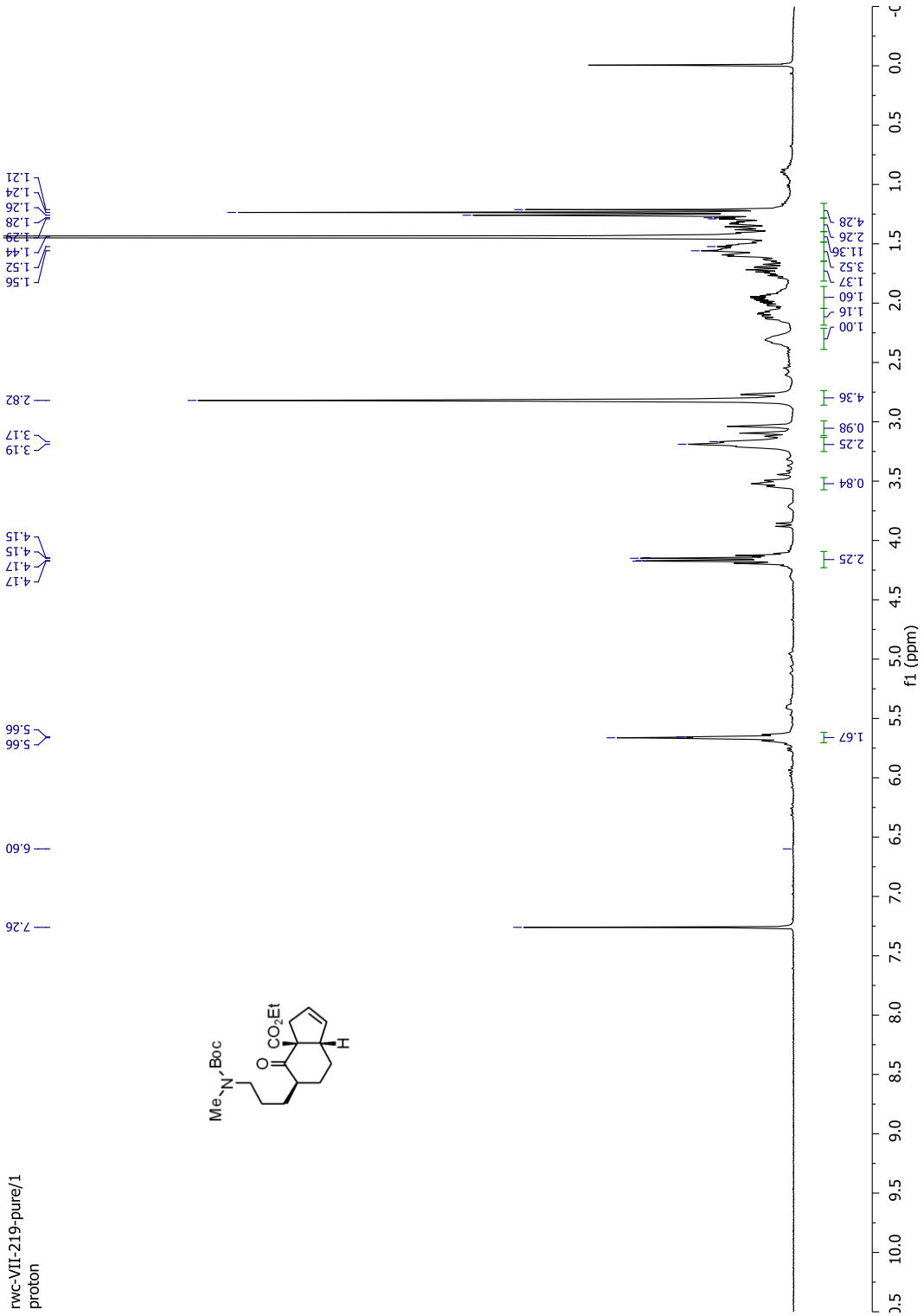
f1 (ppm)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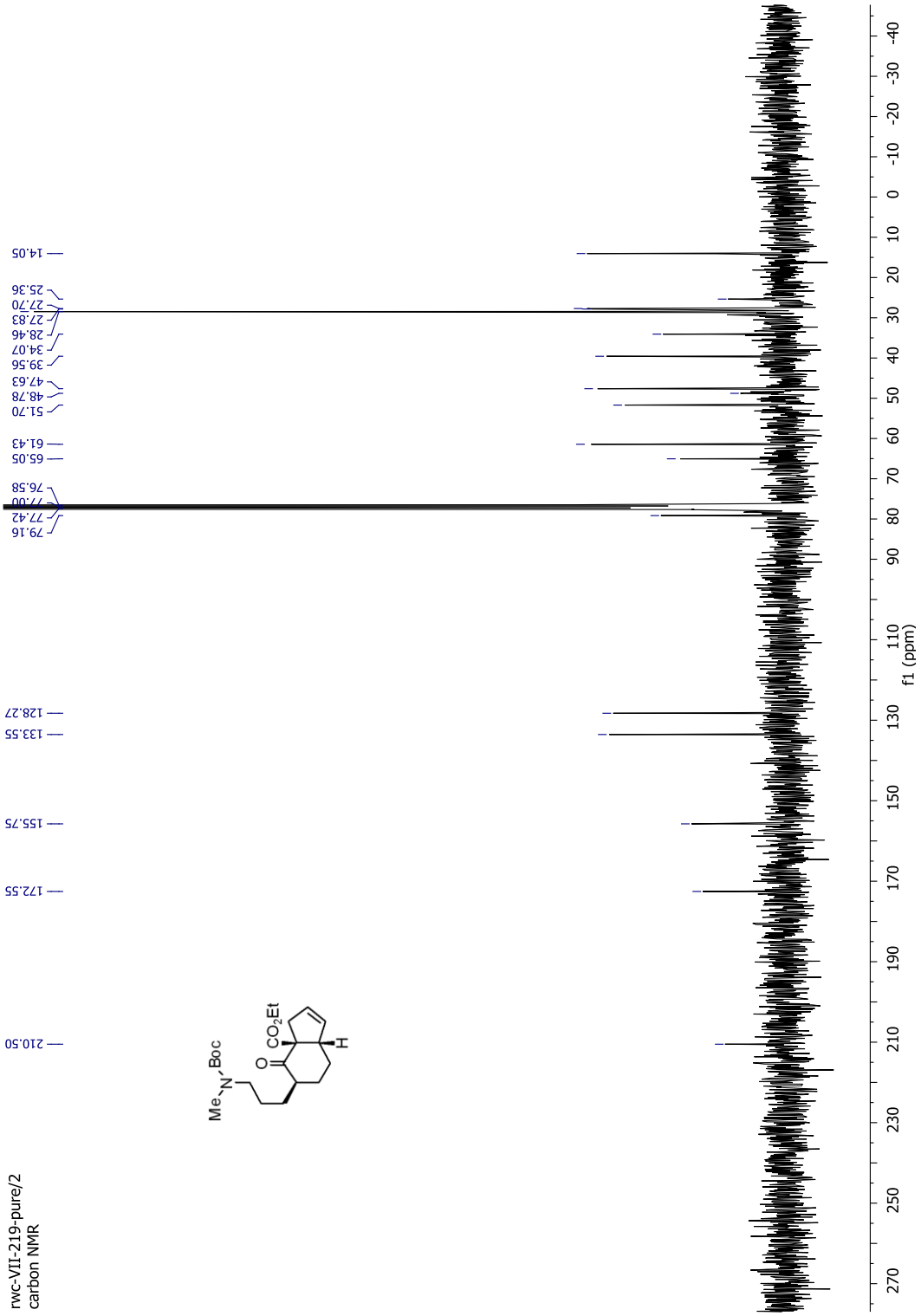
N
Boc
O
CO2Et
H
f1 (ppm)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65.05
76.58
77.00
77.42
79.16
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155.75
172.55
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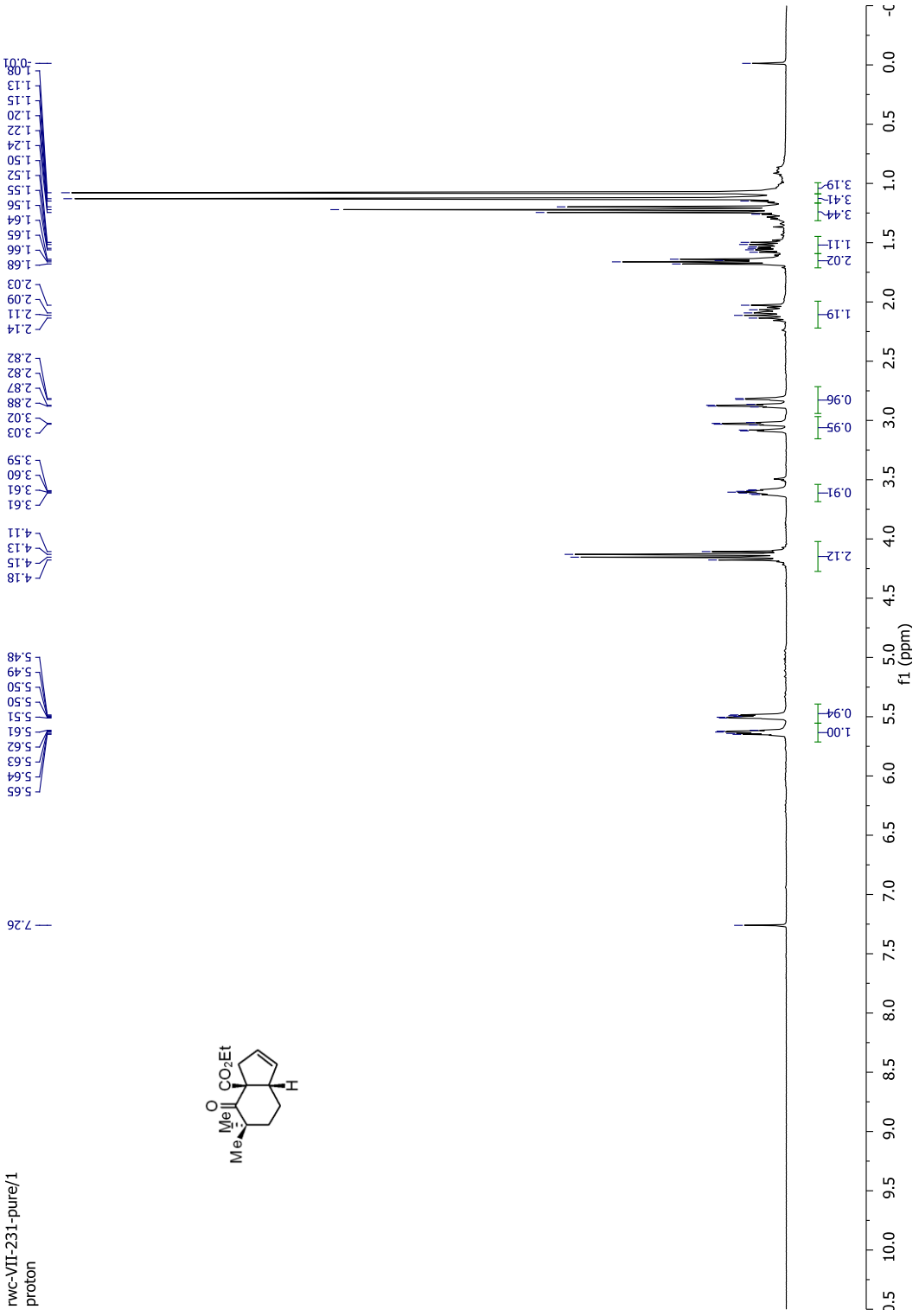
N
Boc
O
CO2Et
H
f1 (ppm)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Me
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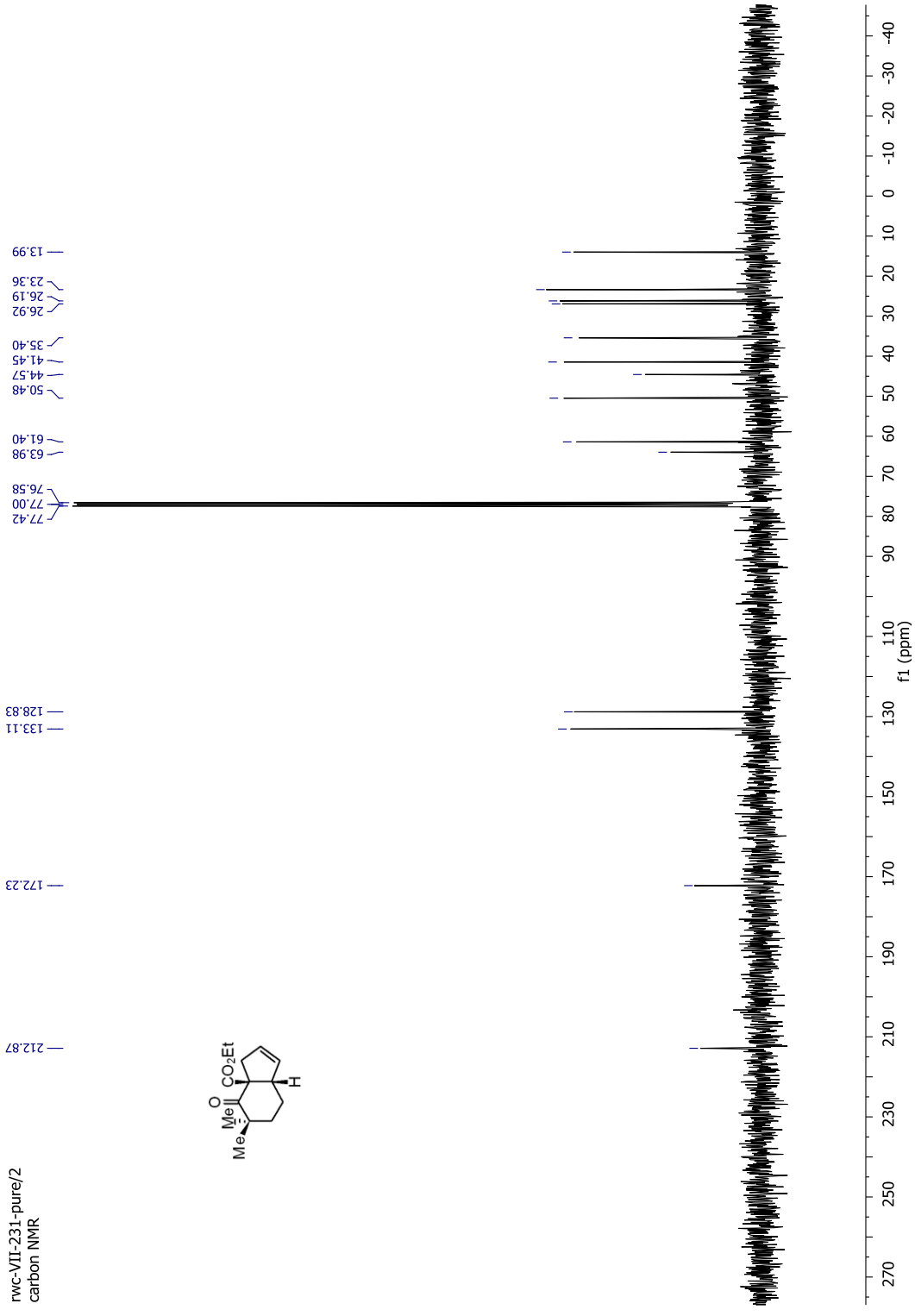
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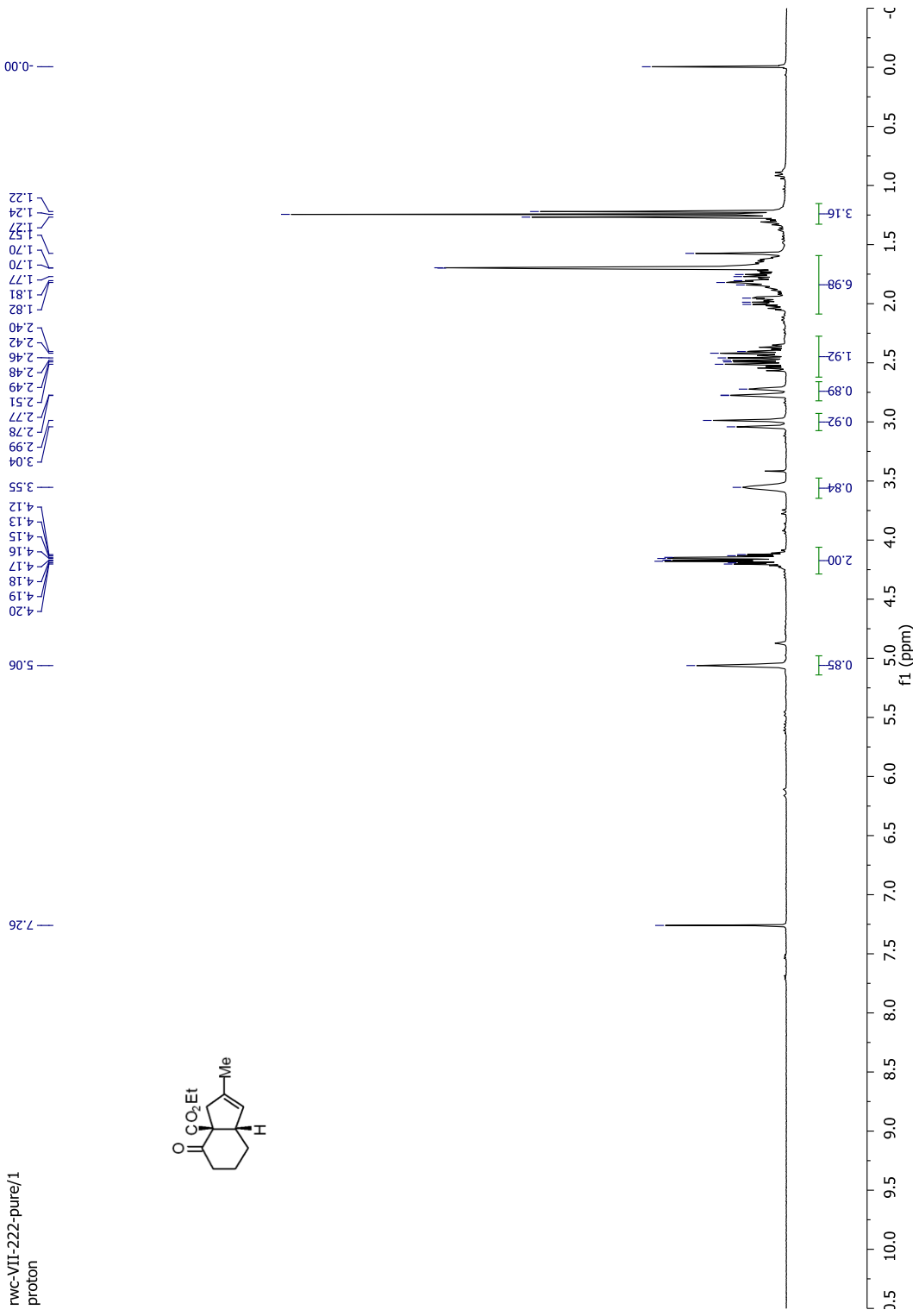
CO2Et
H
Me
O
Me
f1 (ppm)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CO2Et
O
H
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1.27
1.52
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1.82
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2.42
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4.15
4.16
4.17
4.18
4.19
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0.85
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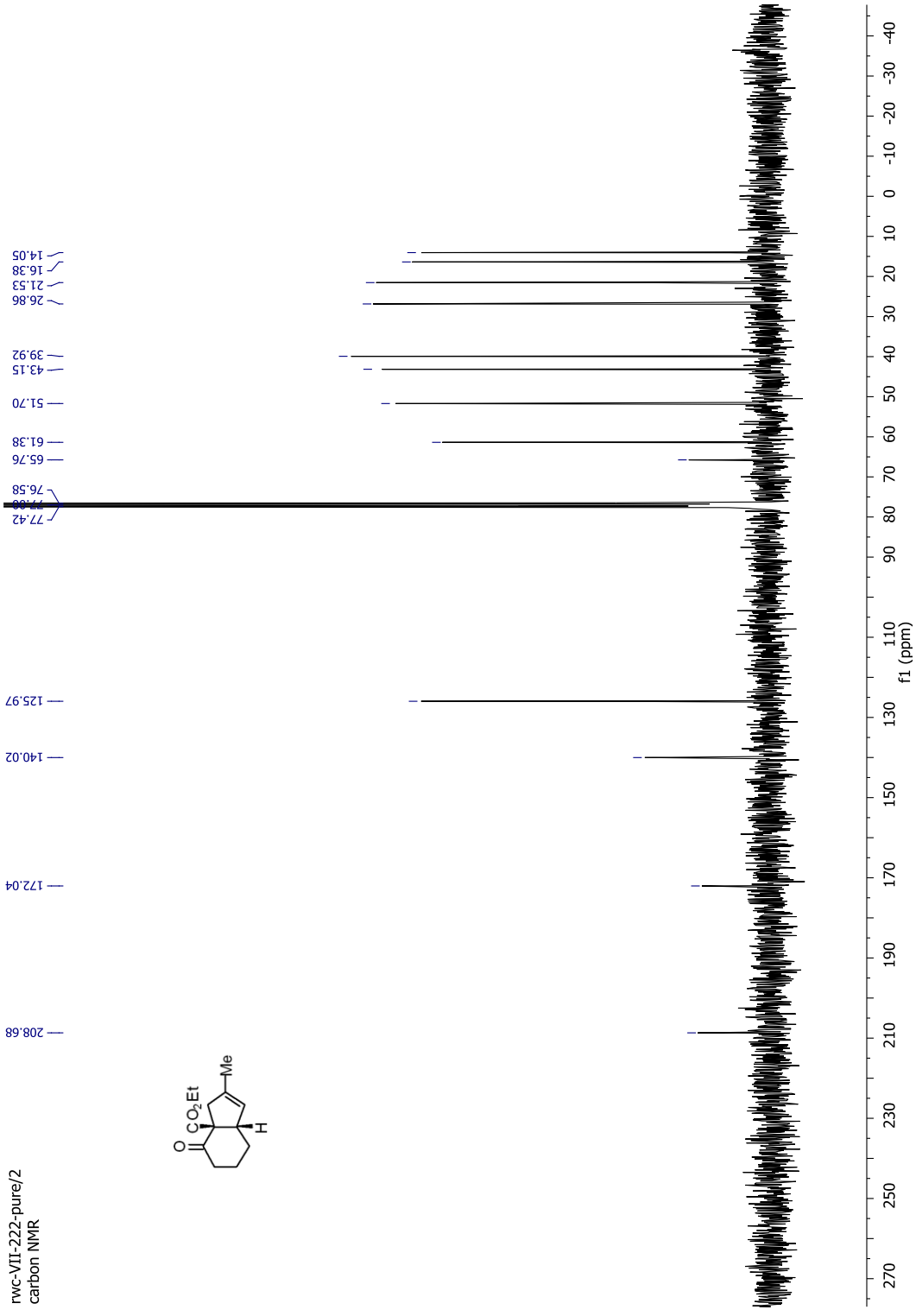
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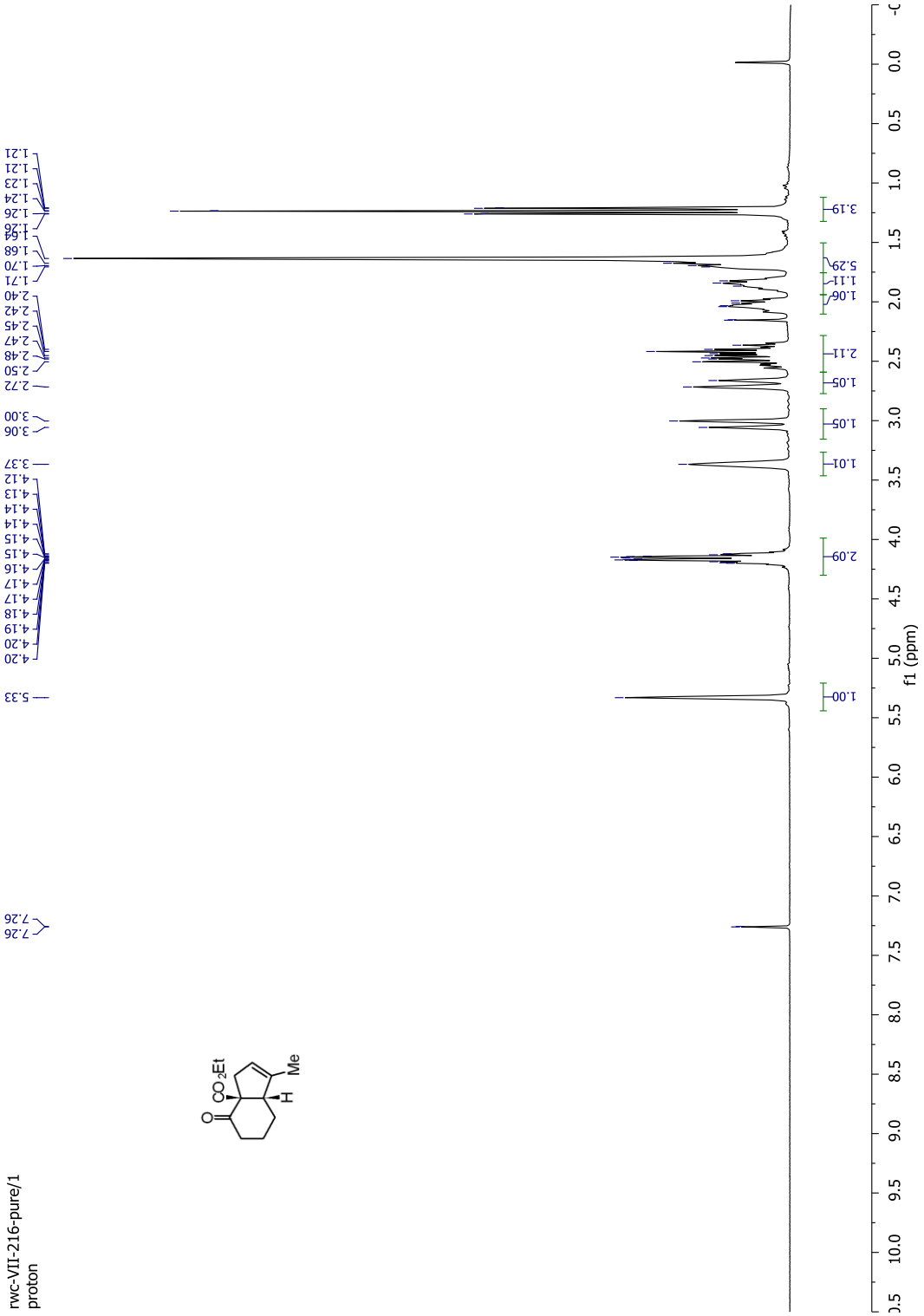
77.42
125.97
140.02
172.04
208.68
Me
CO2Et
O
H
f1 (ppm)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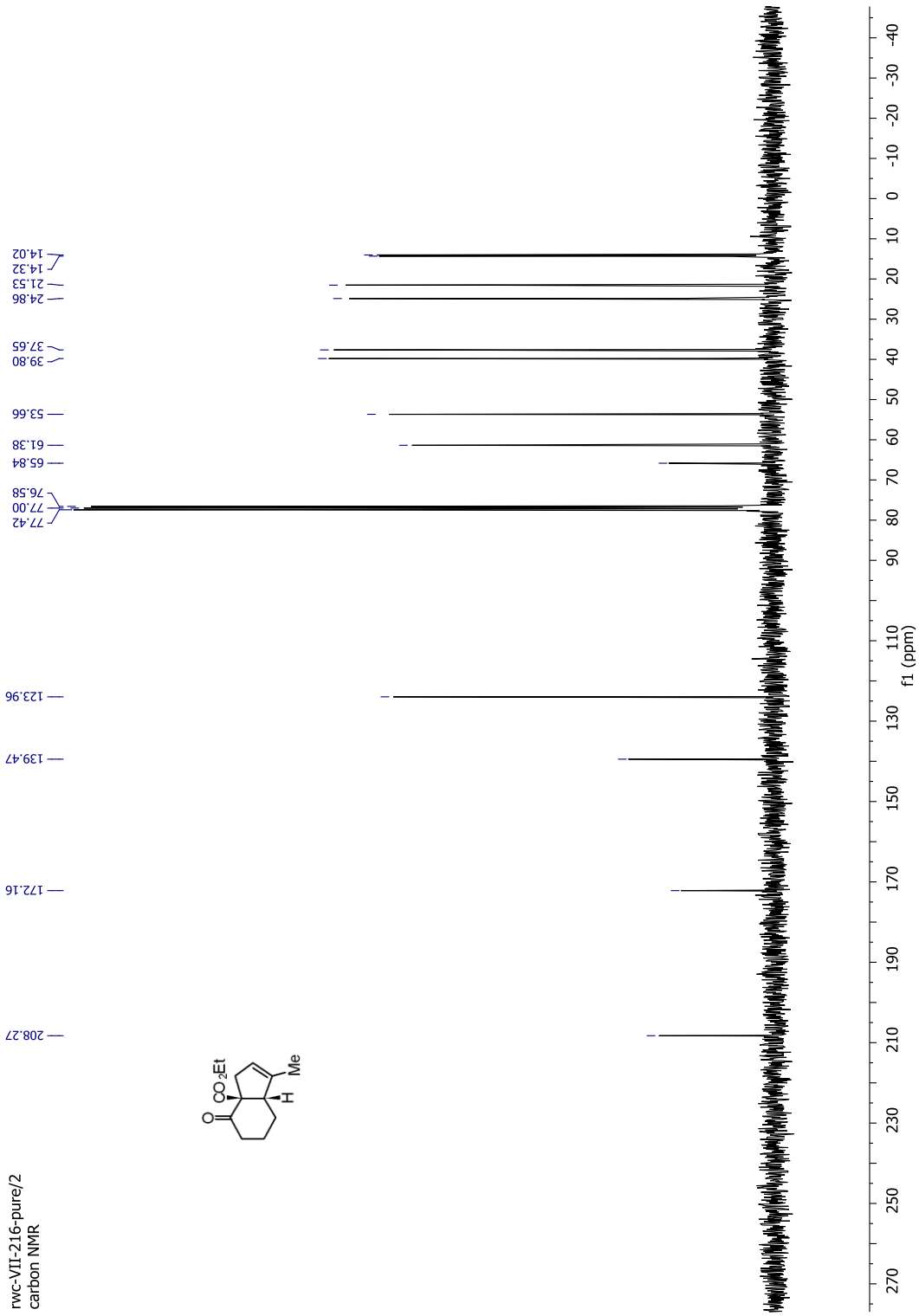
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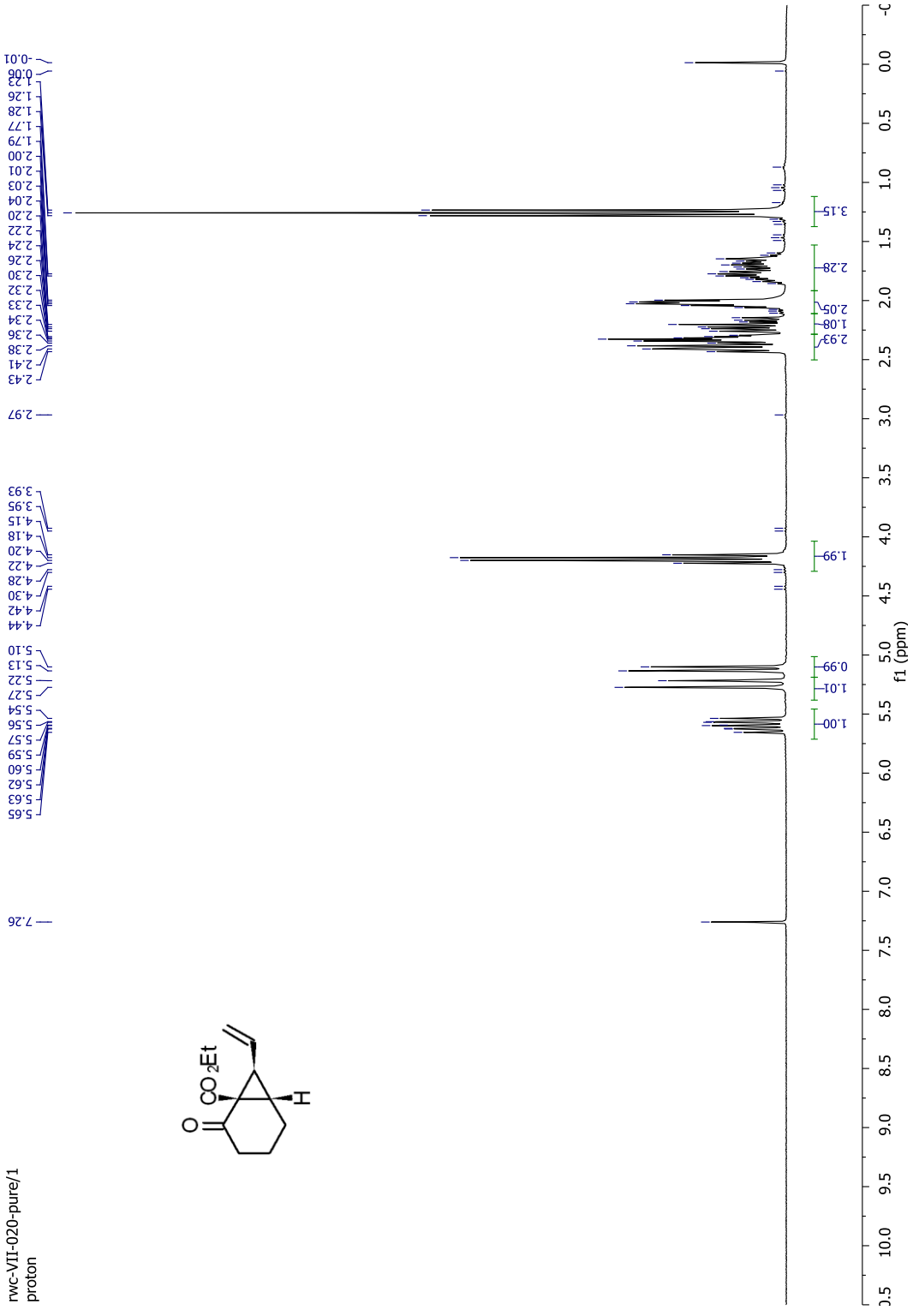
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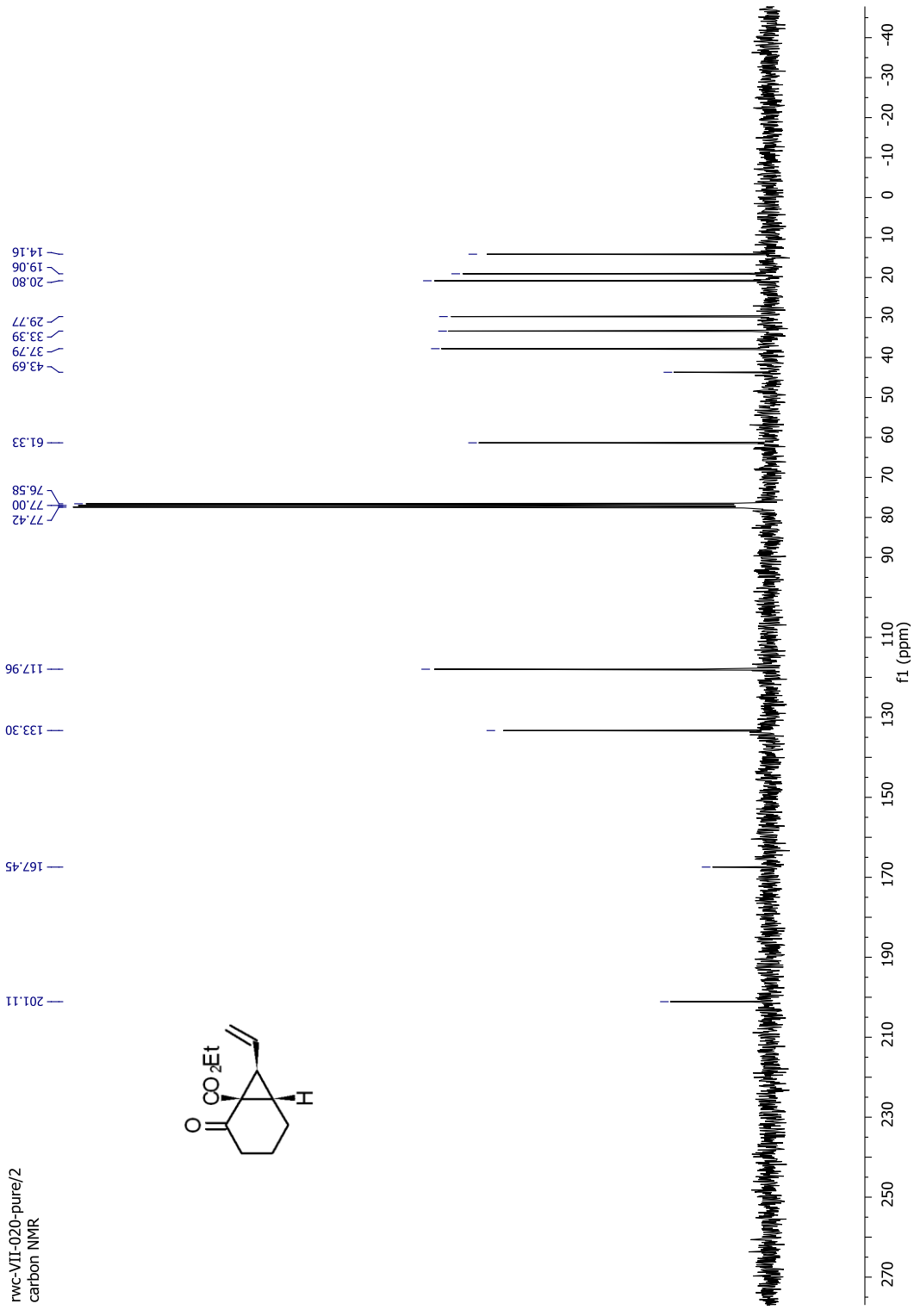
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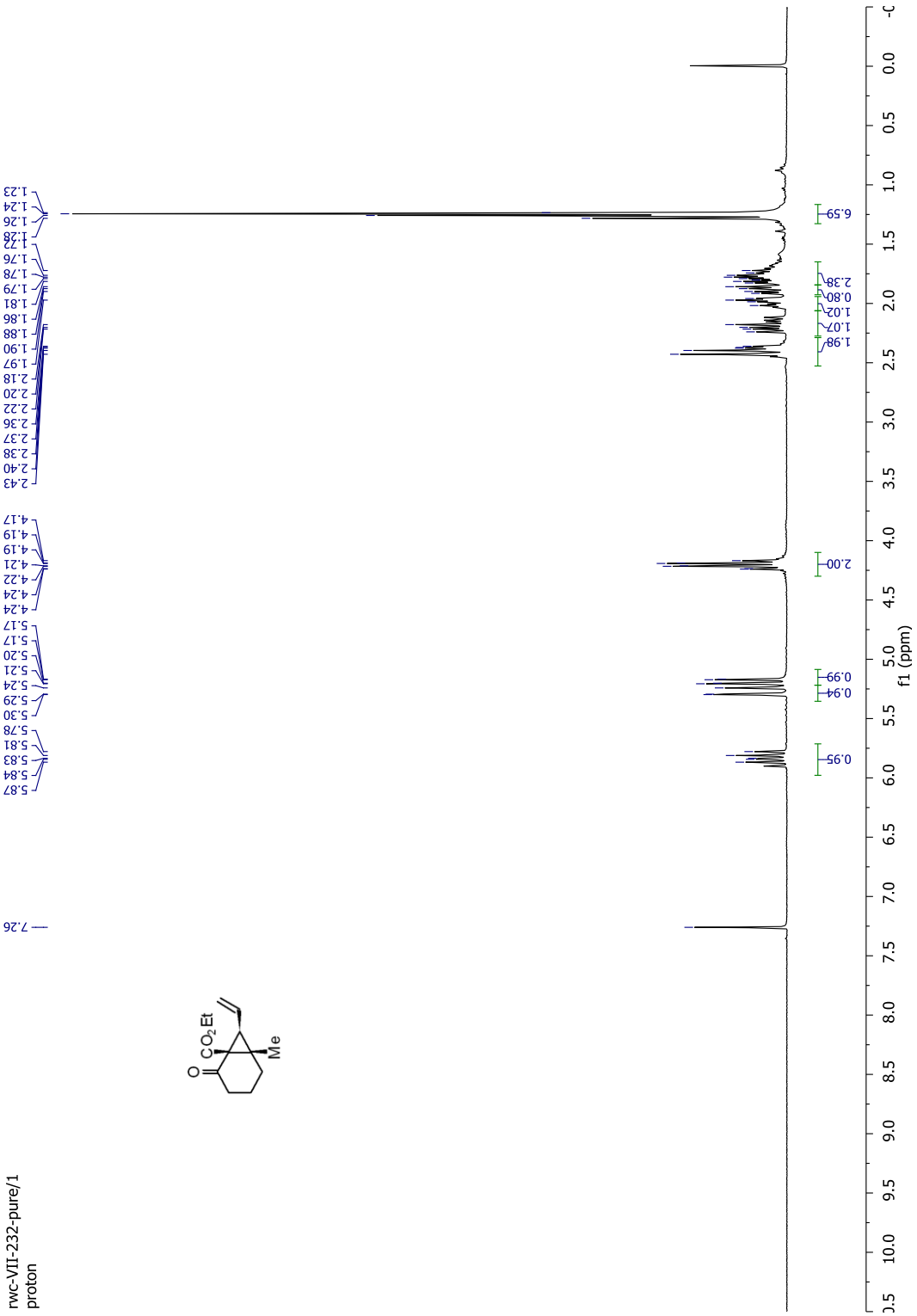
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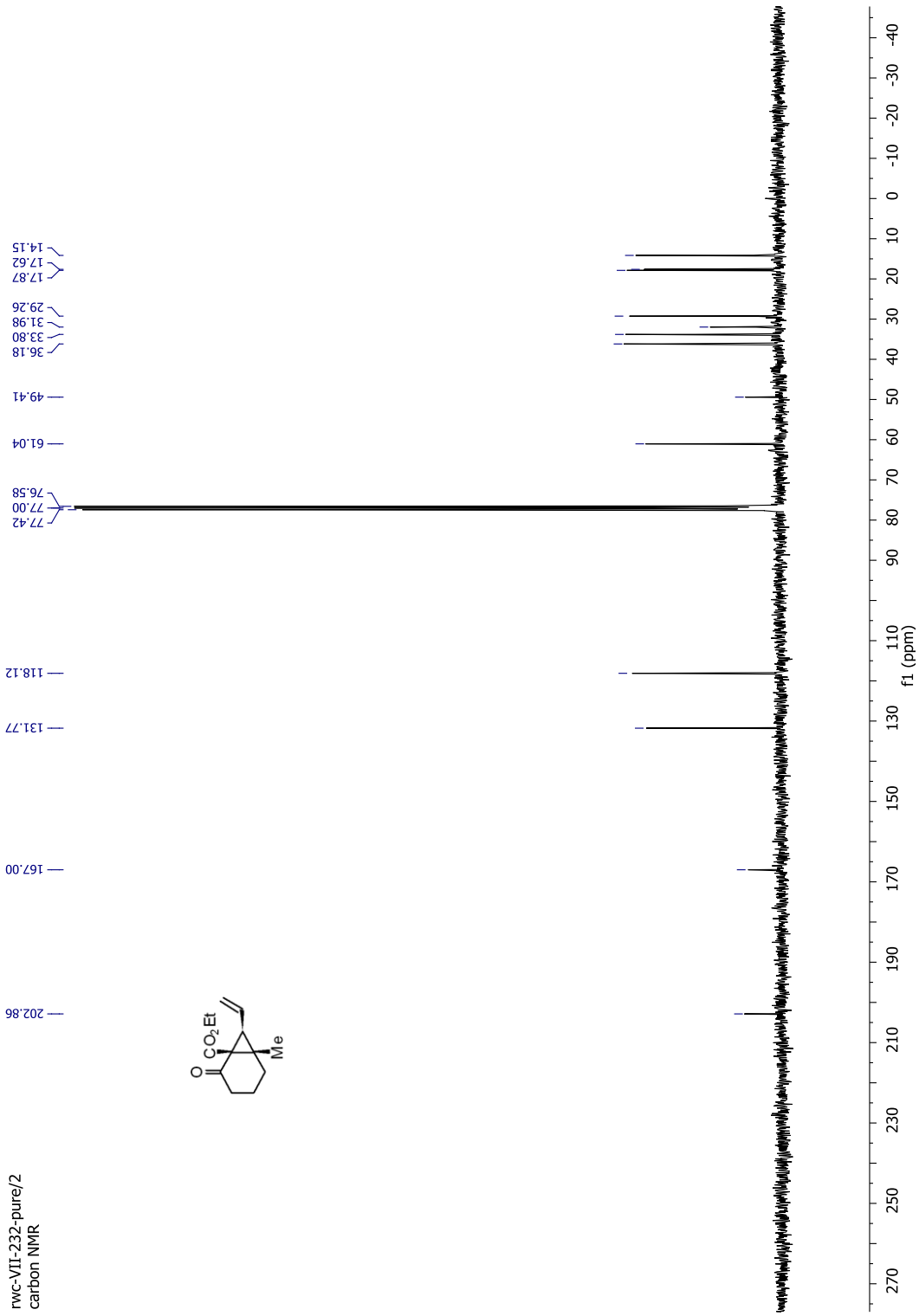
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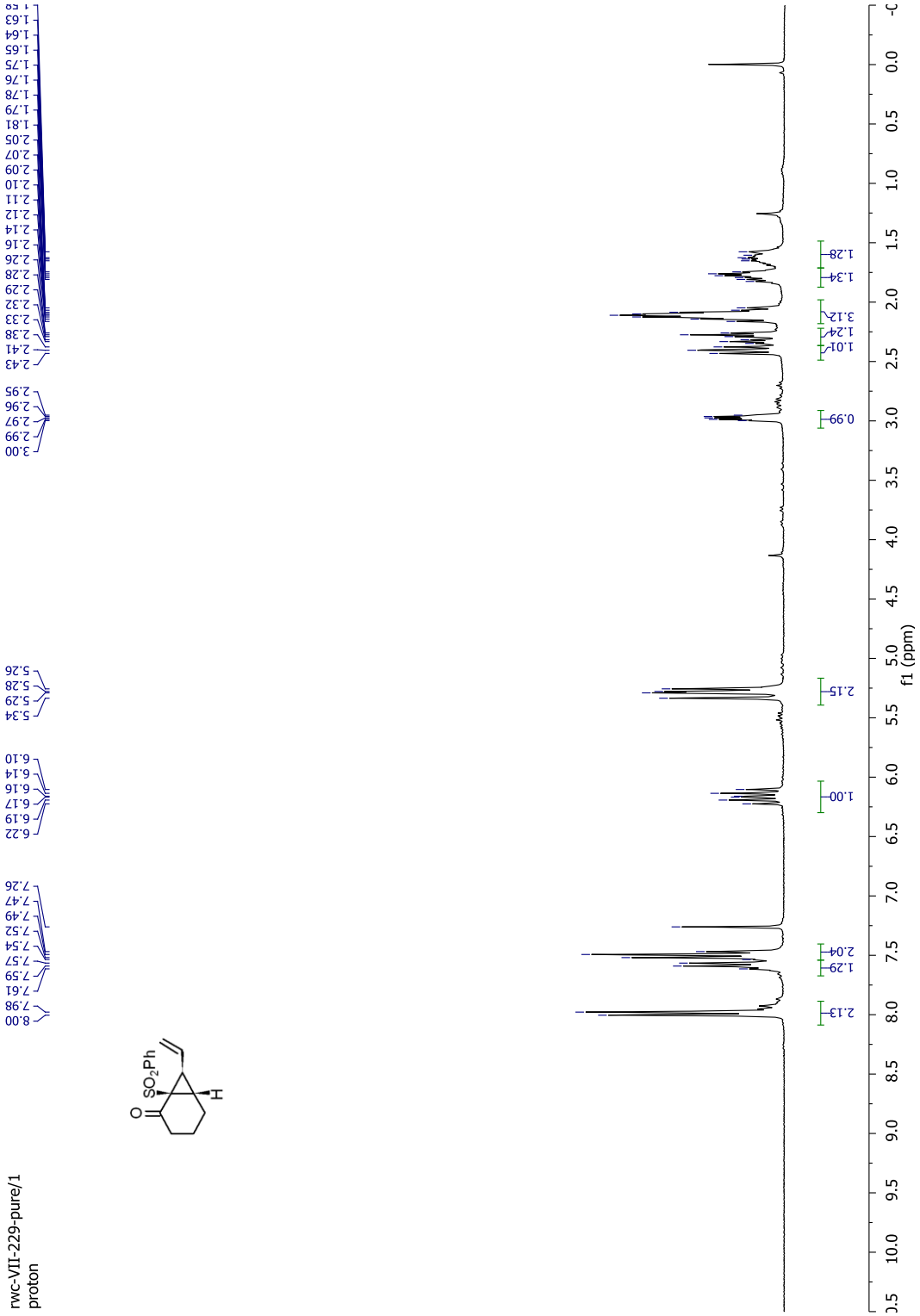
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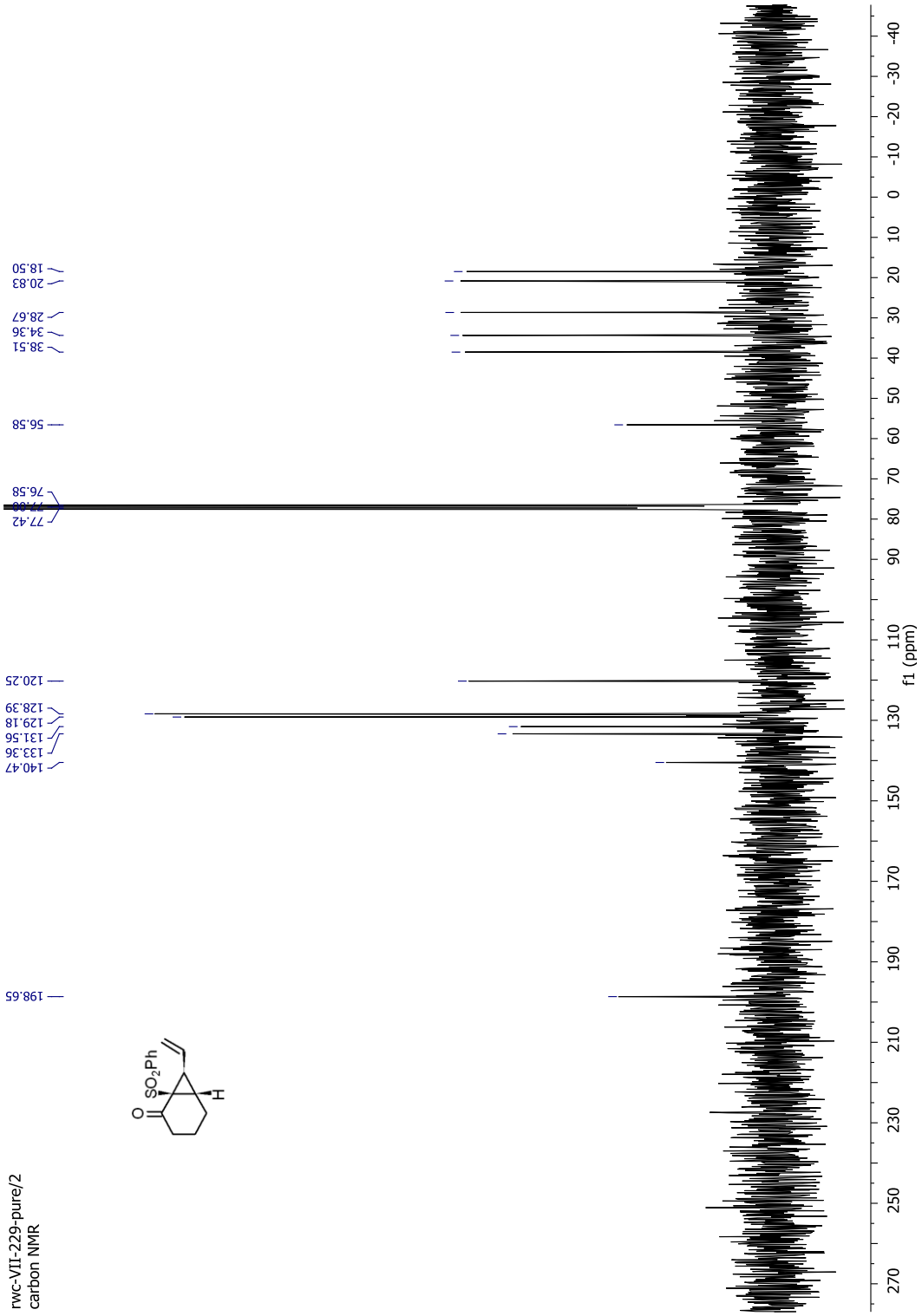
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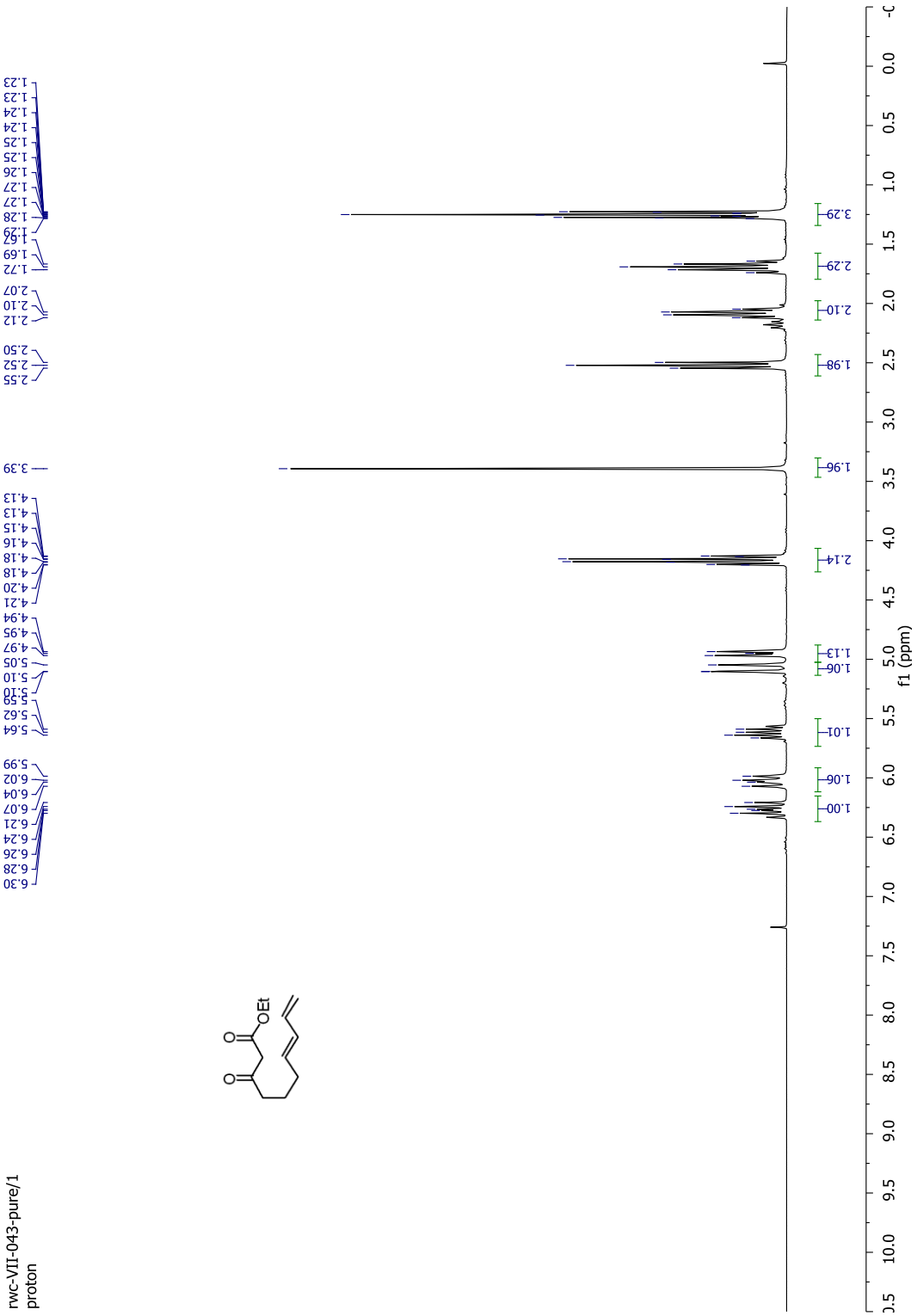
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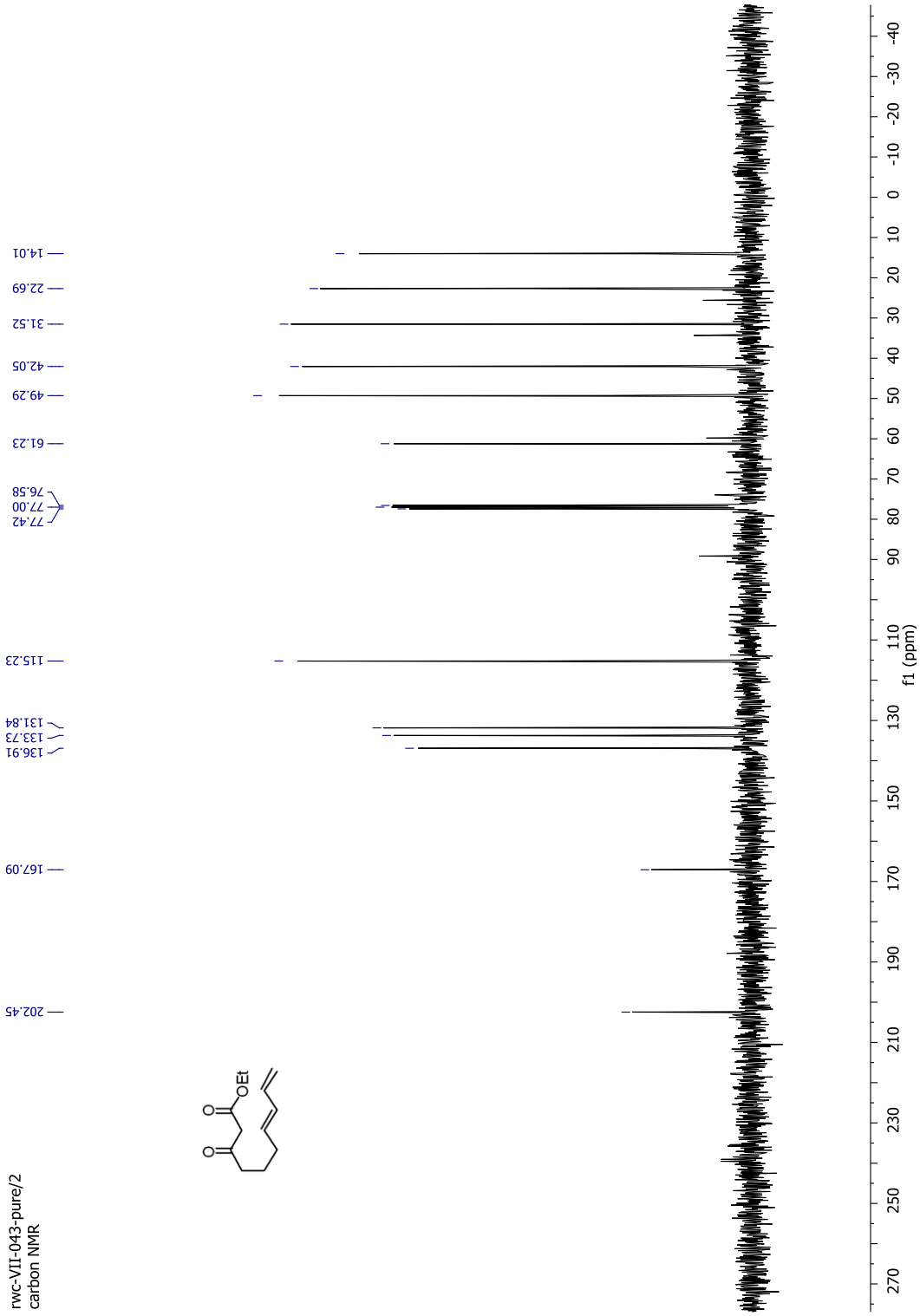
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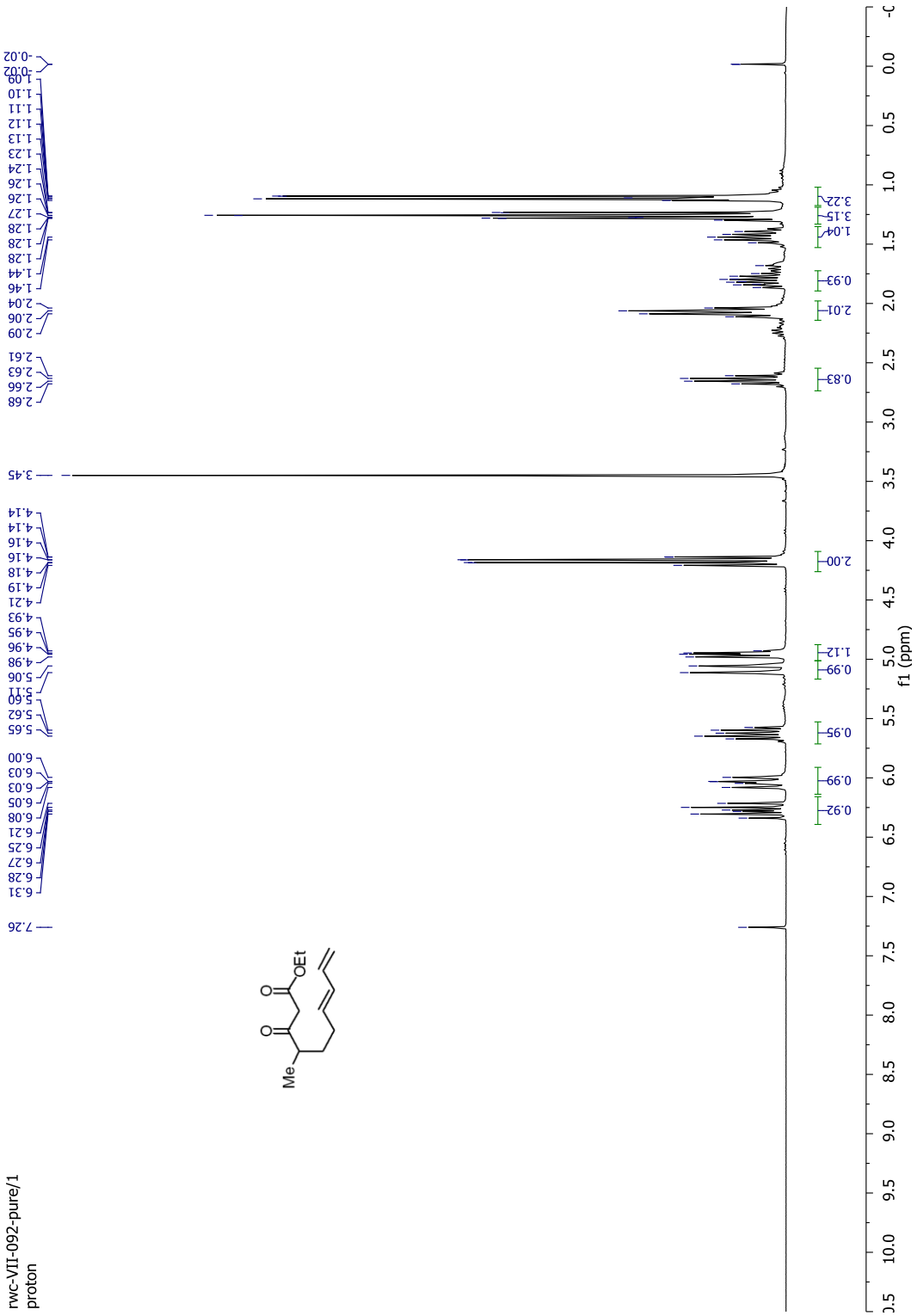
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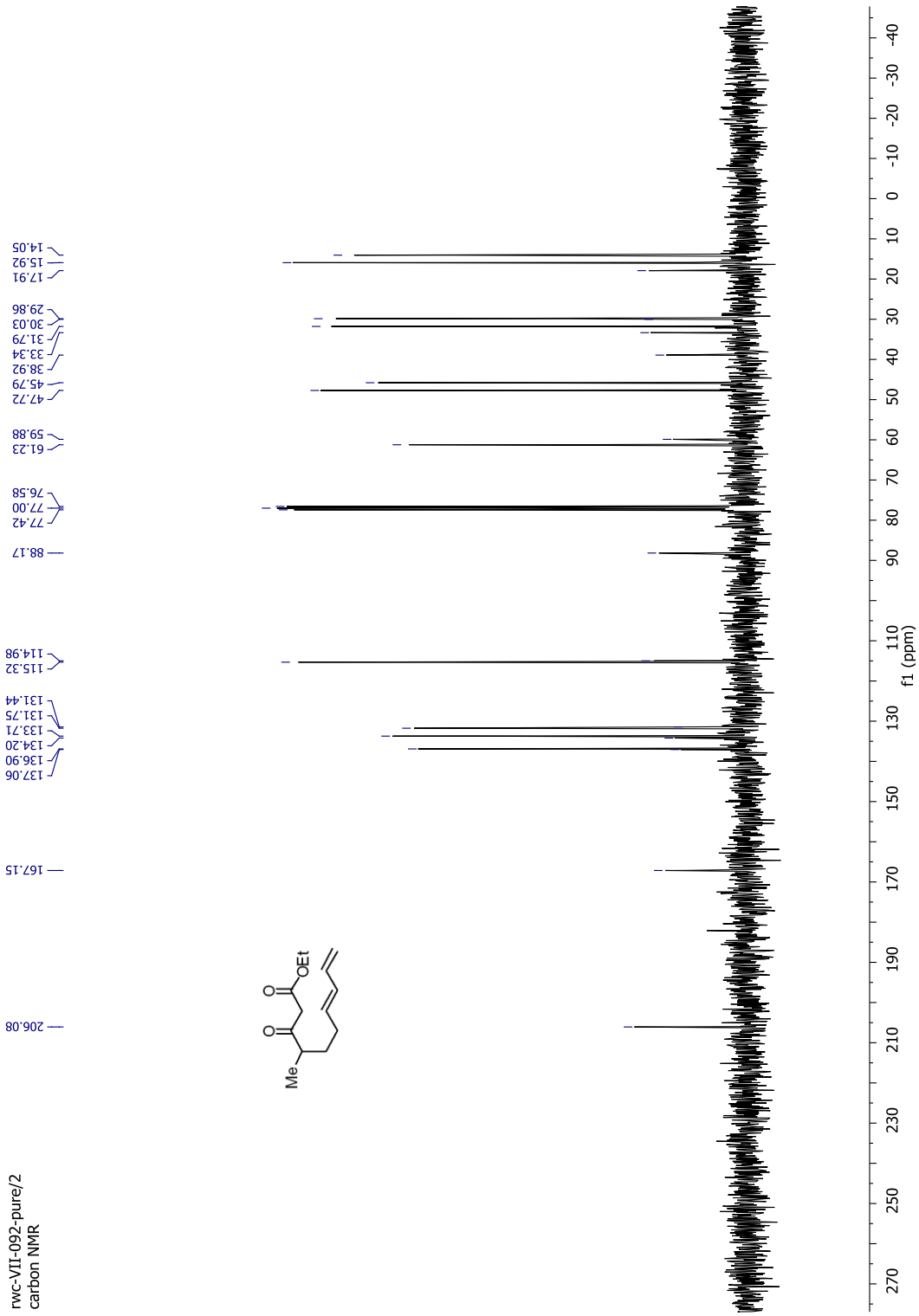
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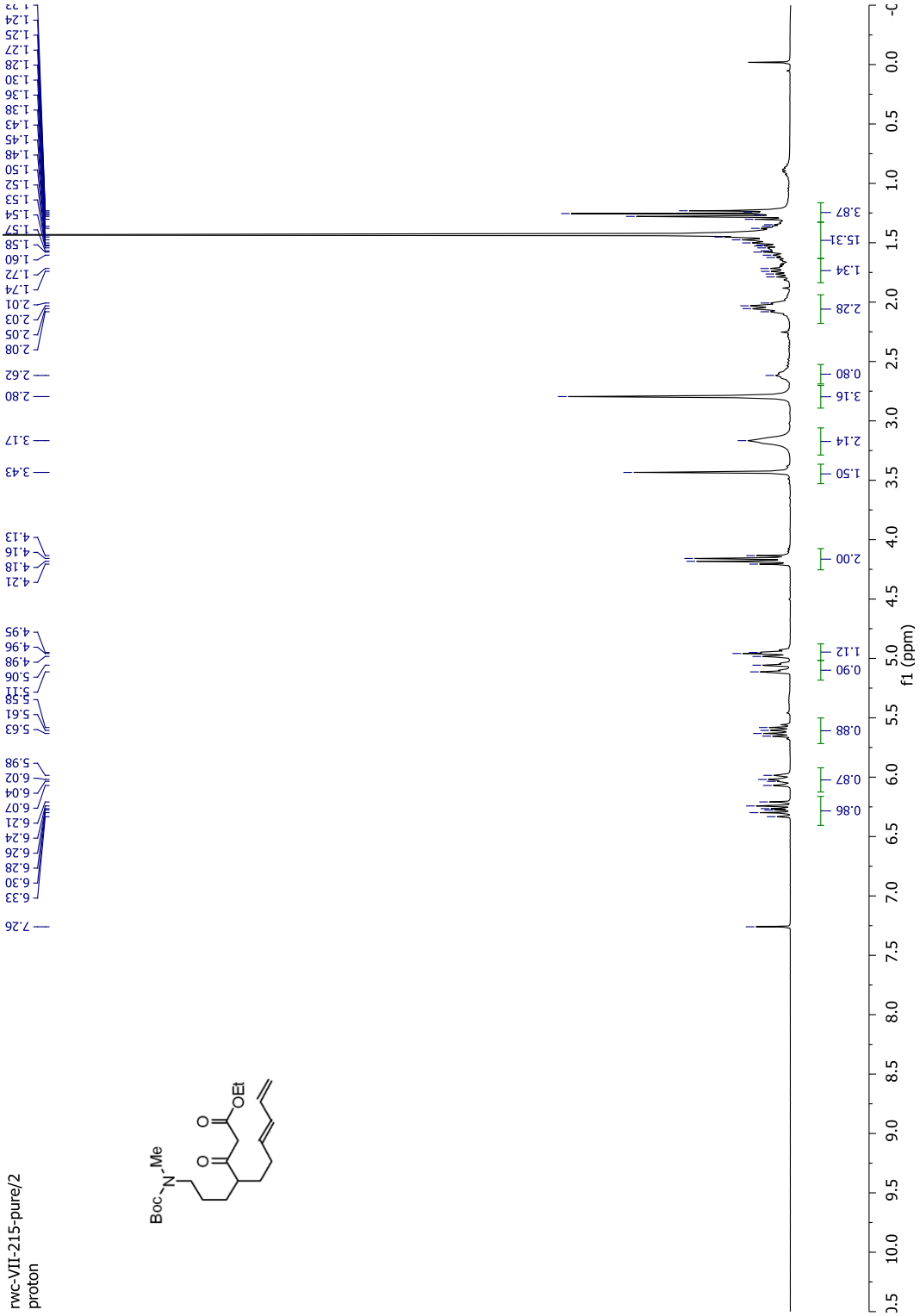
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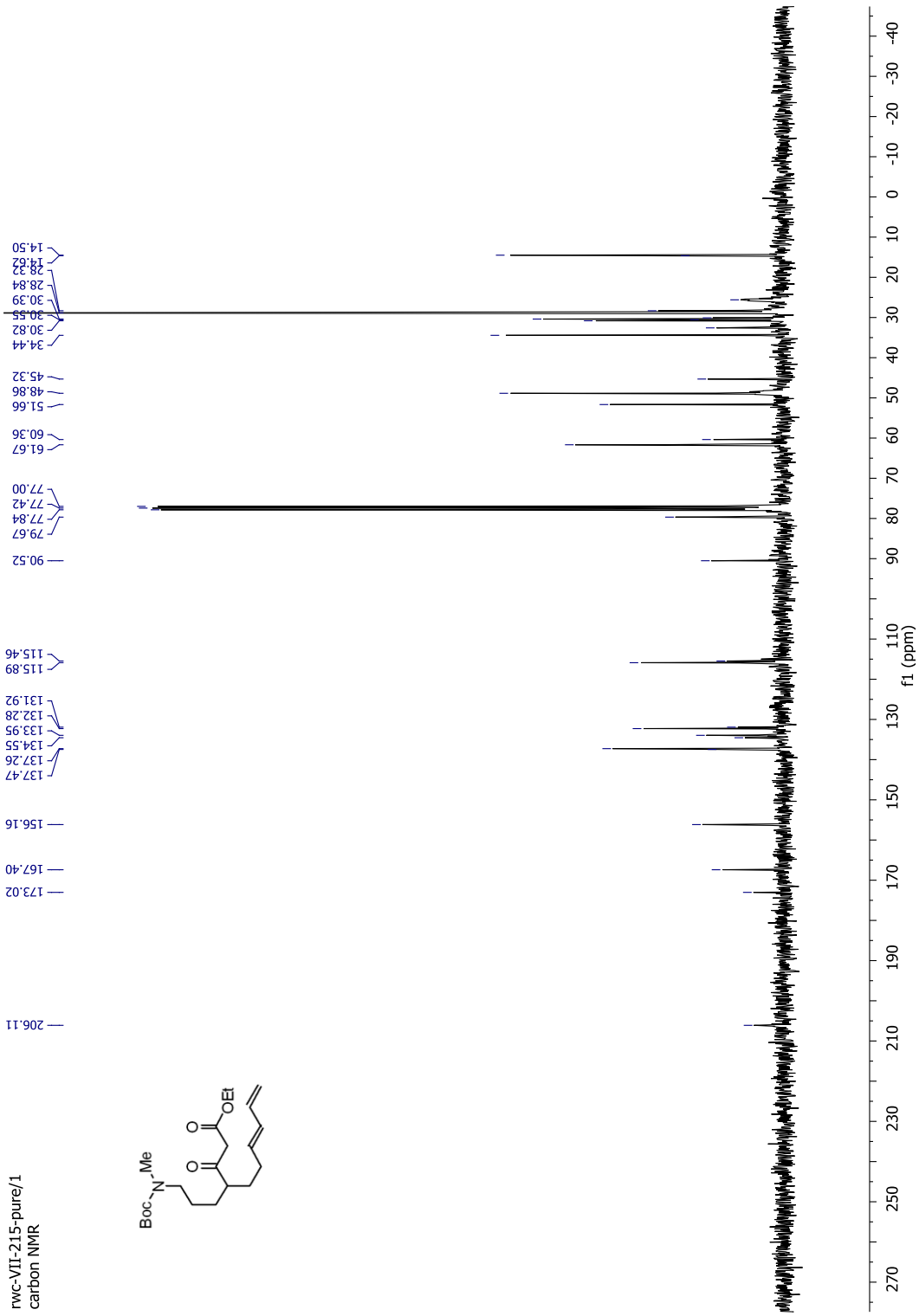
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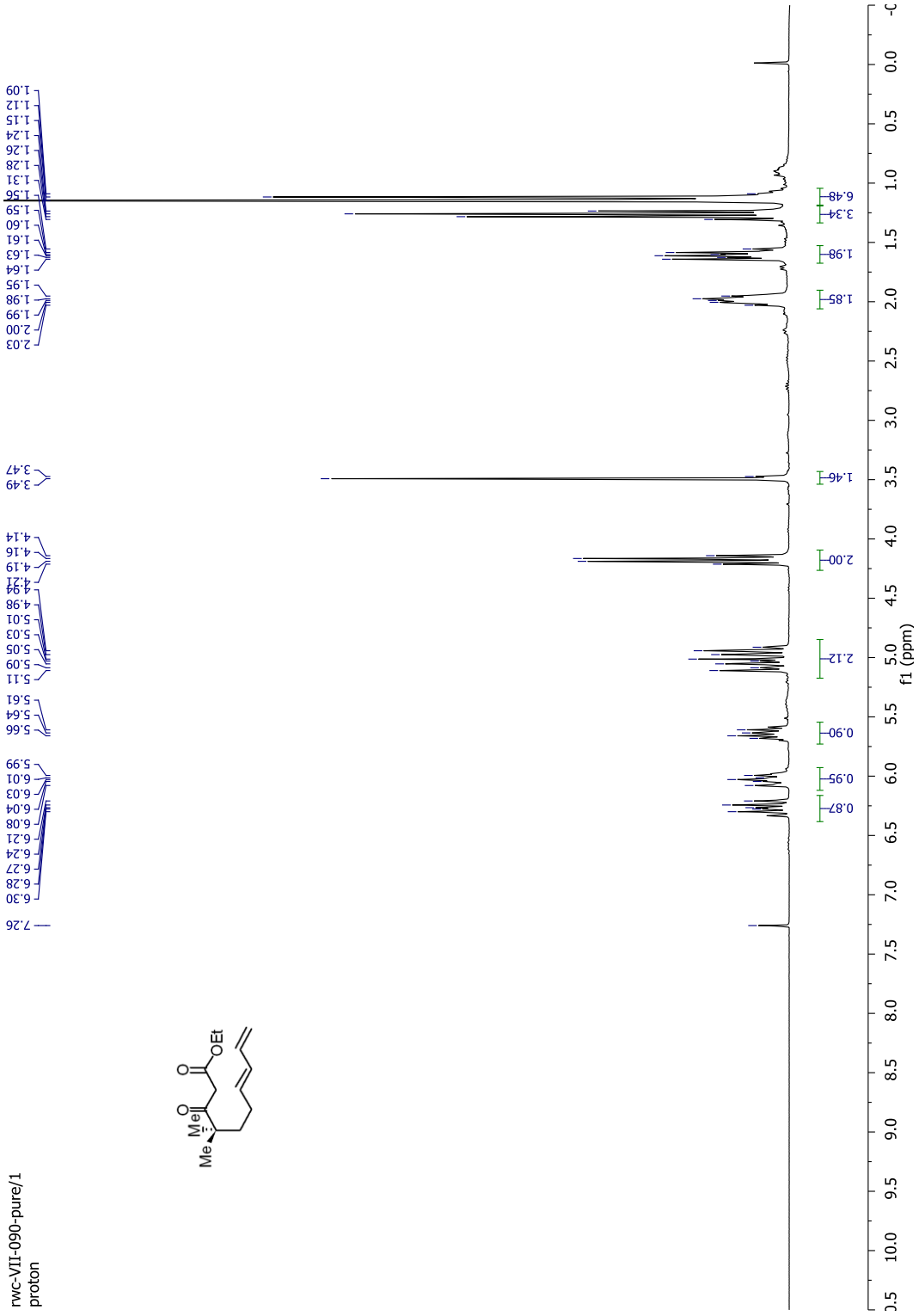
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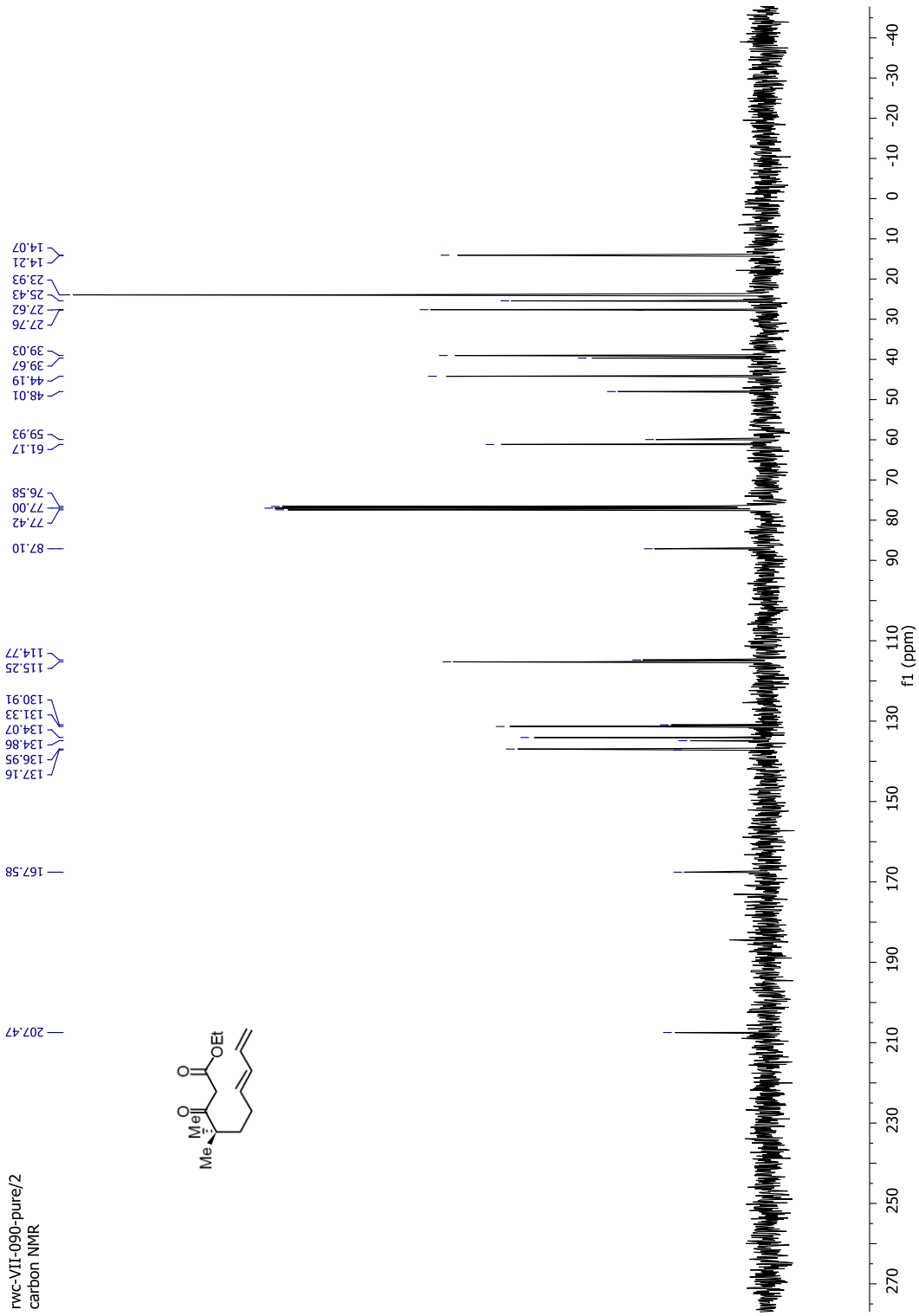
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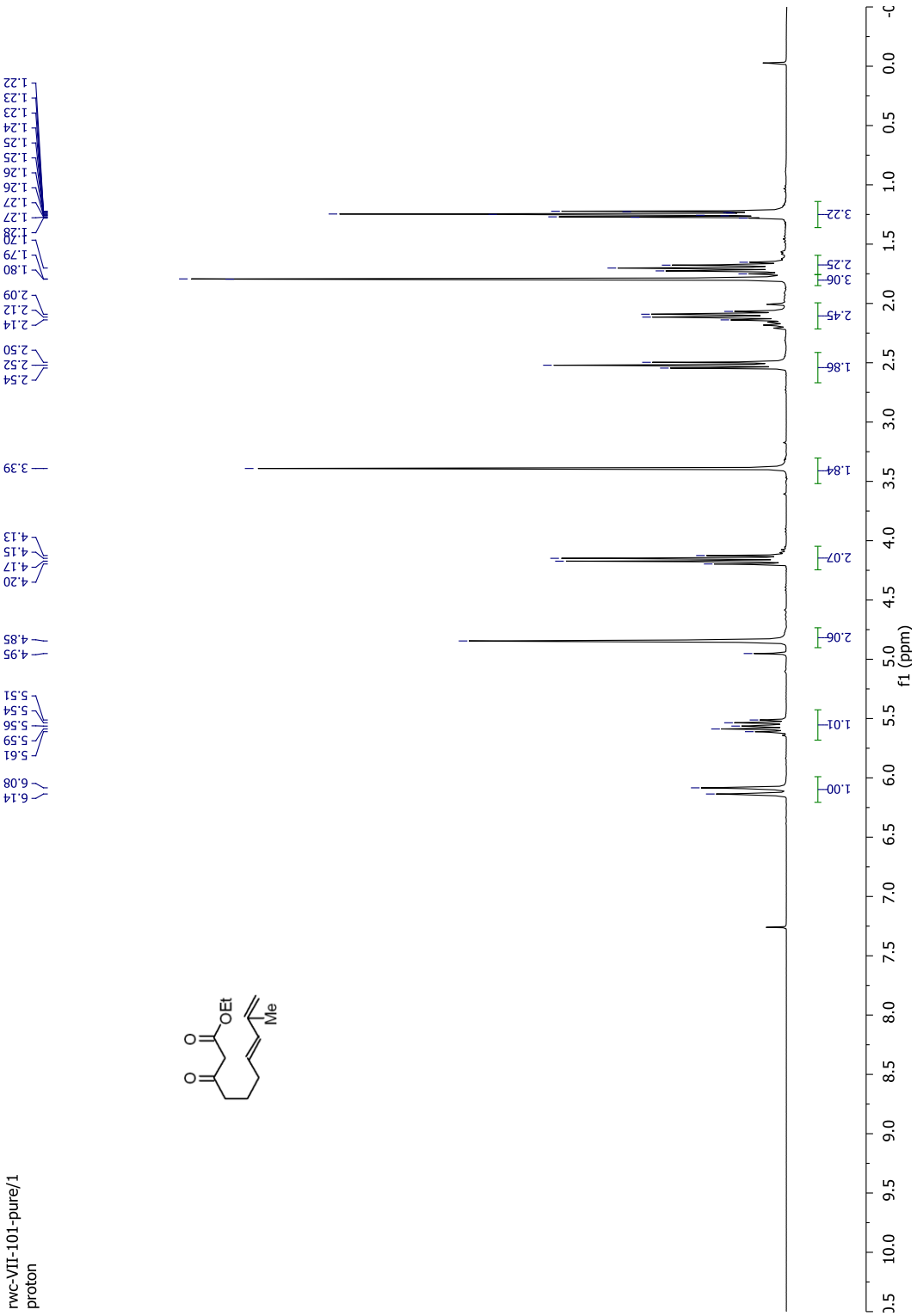
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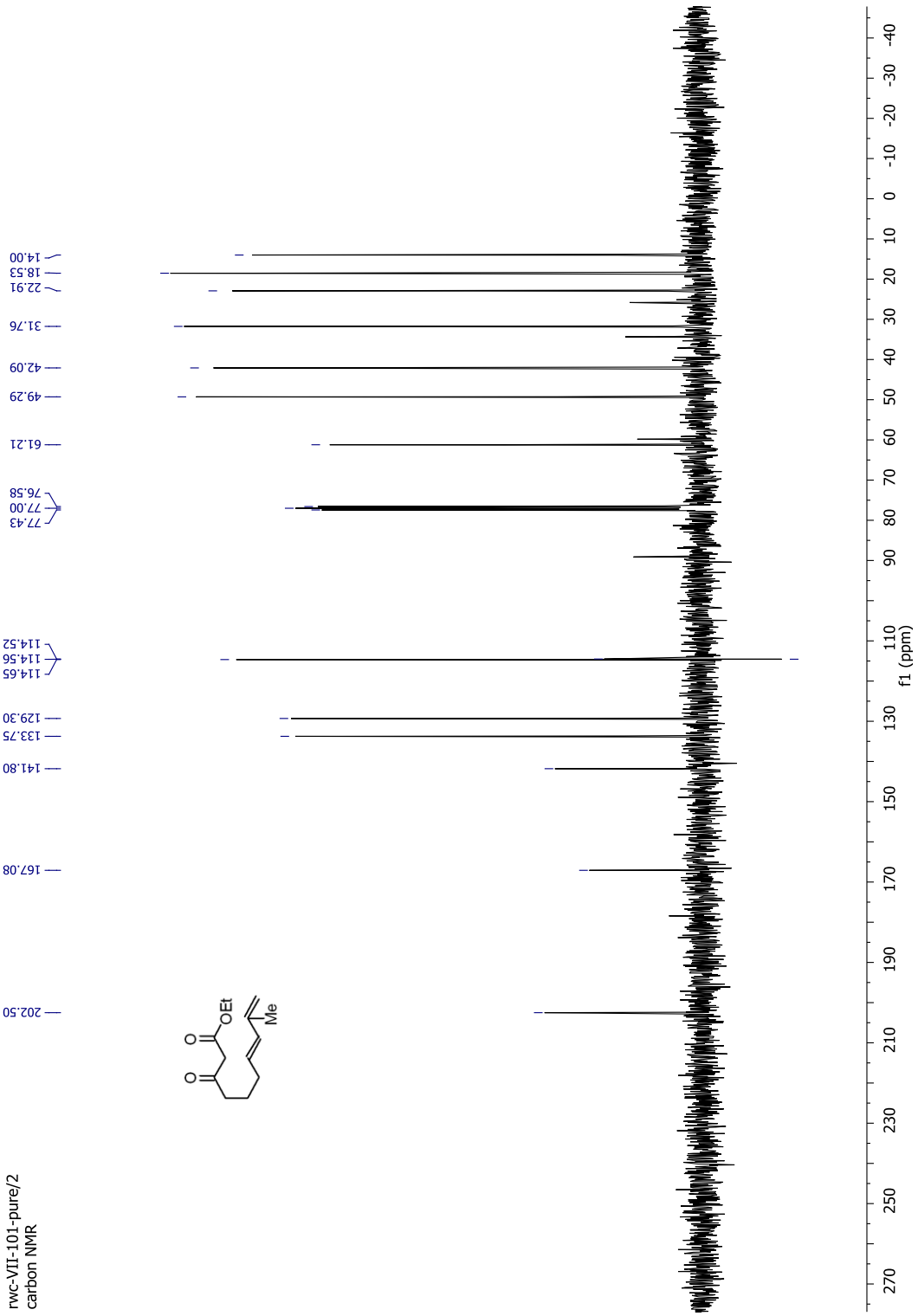
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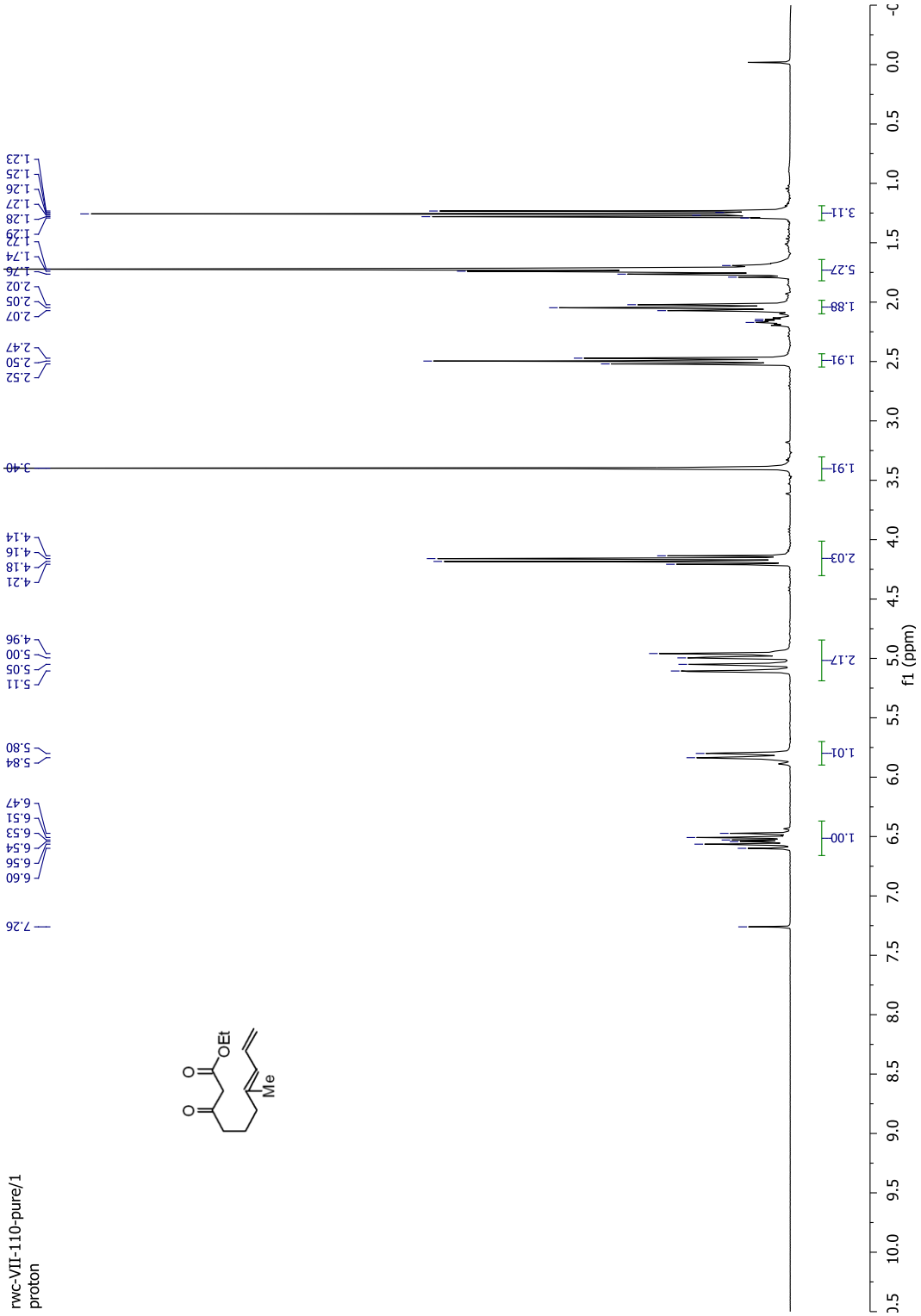
Me
f1 (ppm)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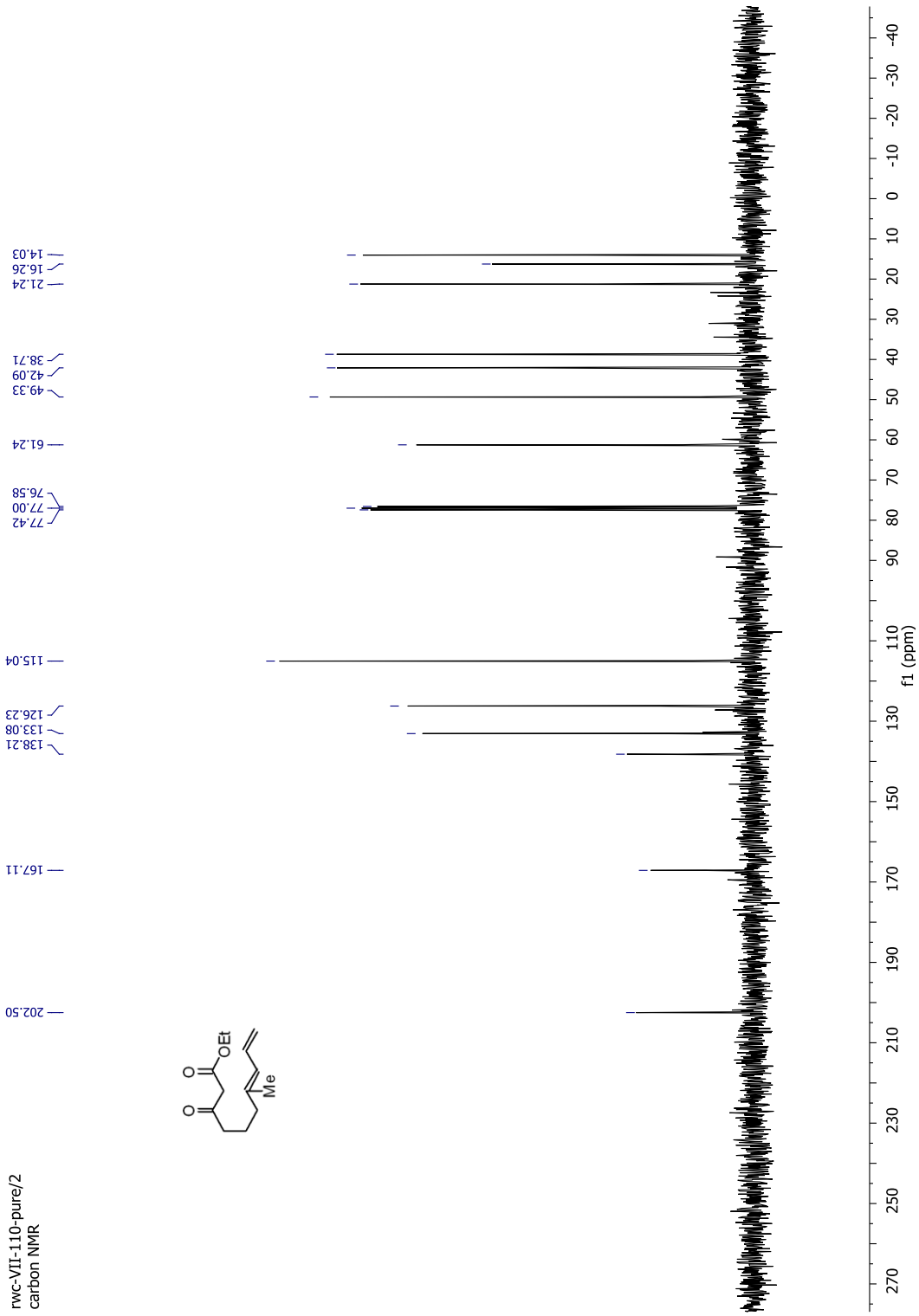
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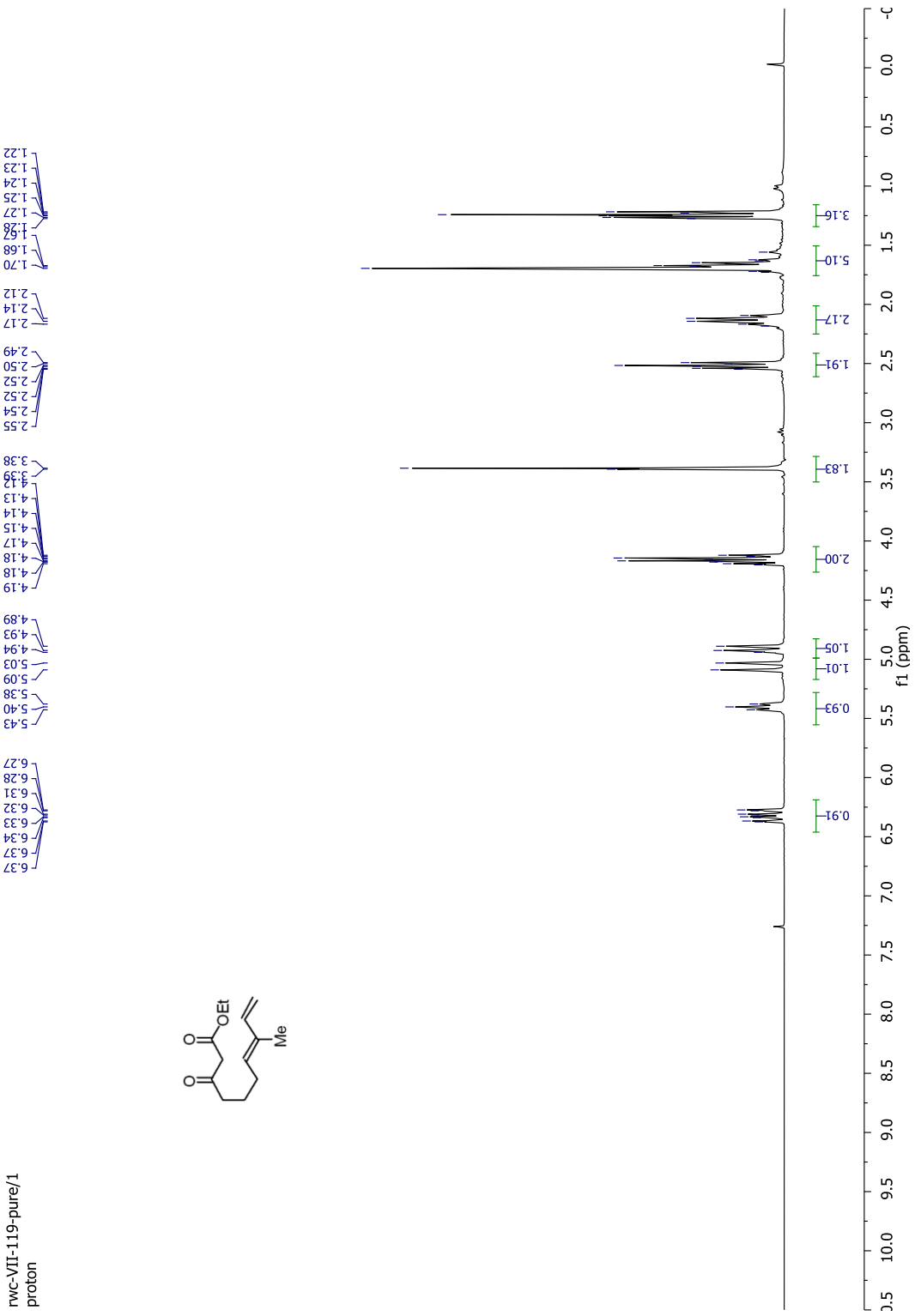
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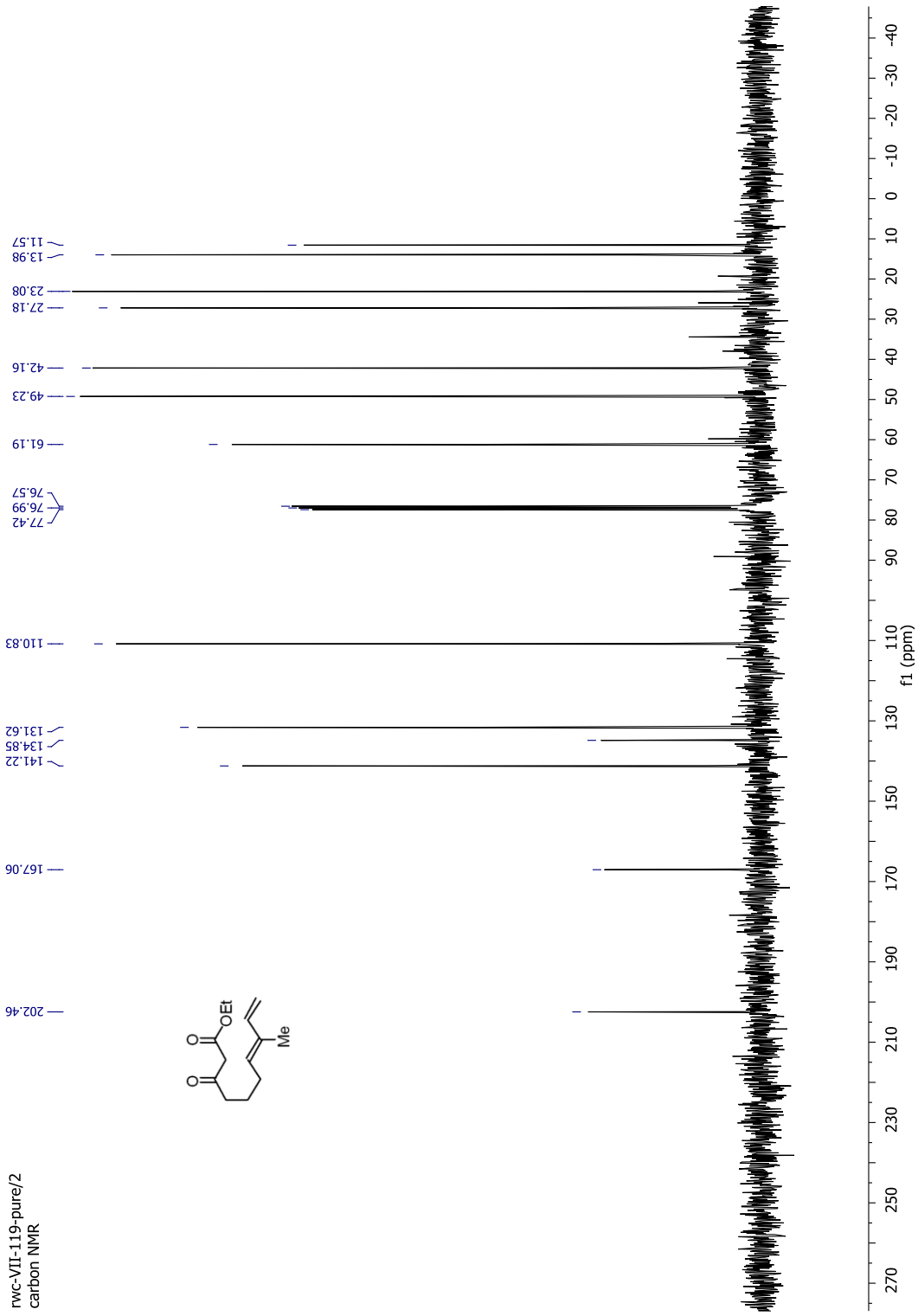
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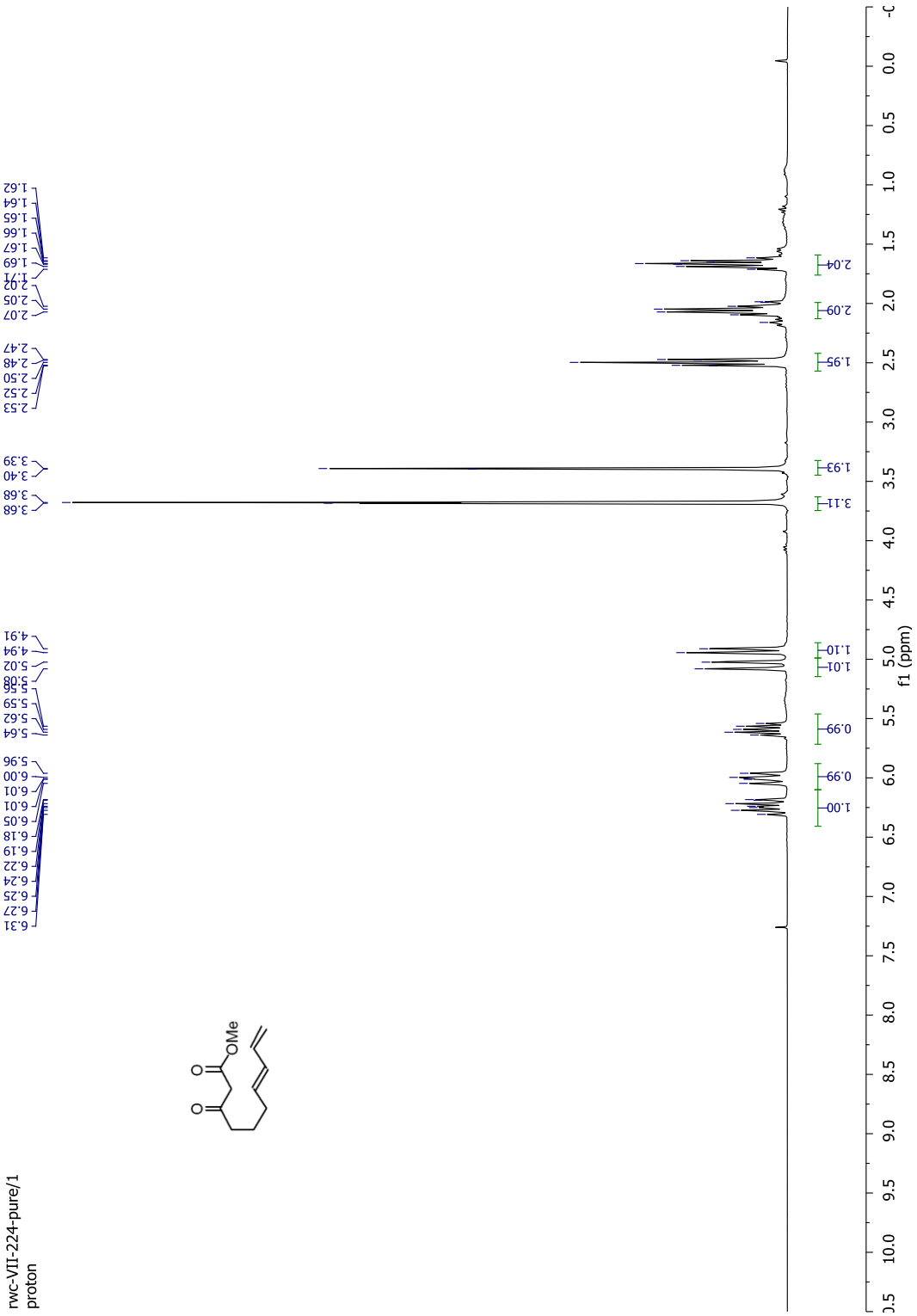
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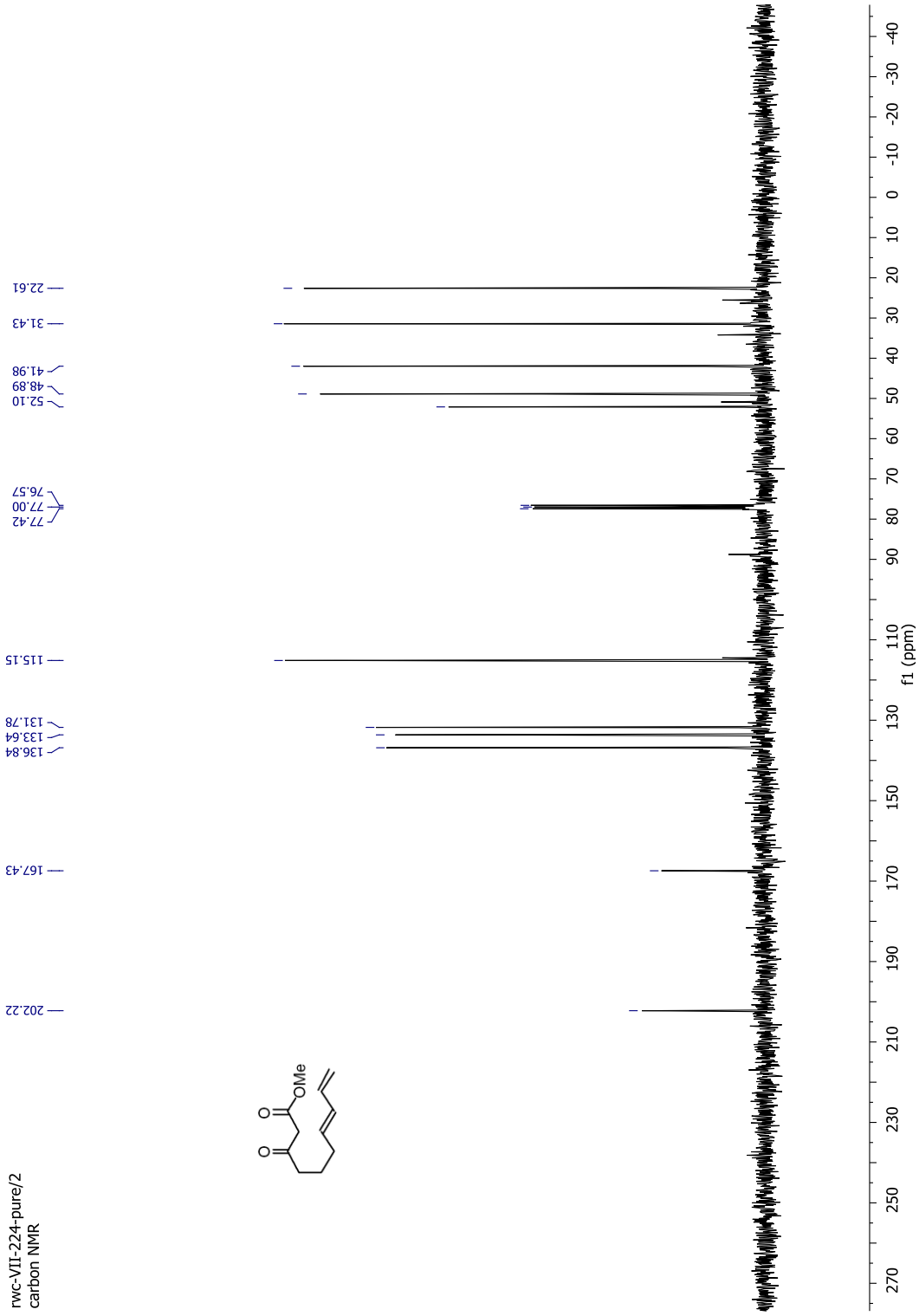
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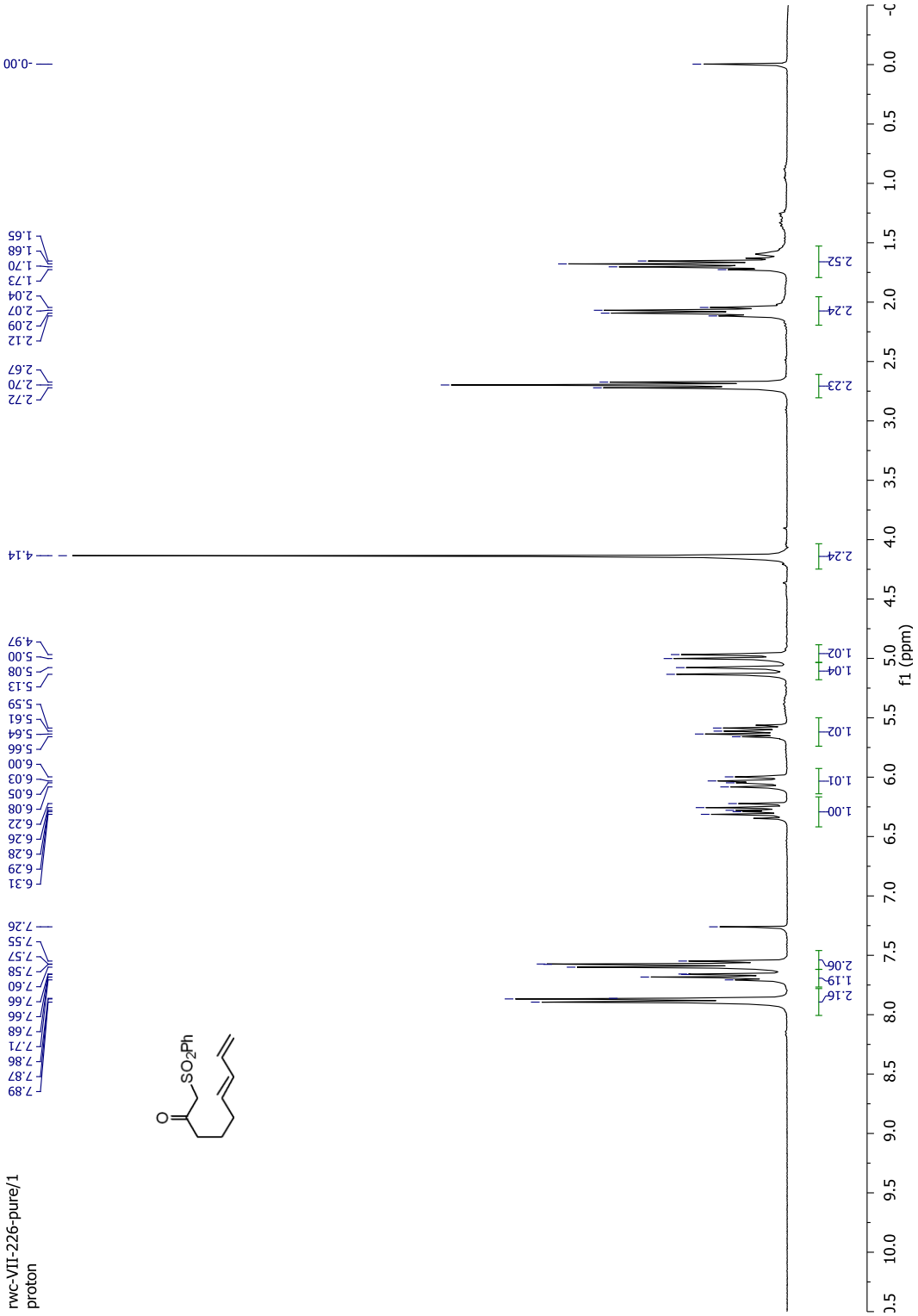
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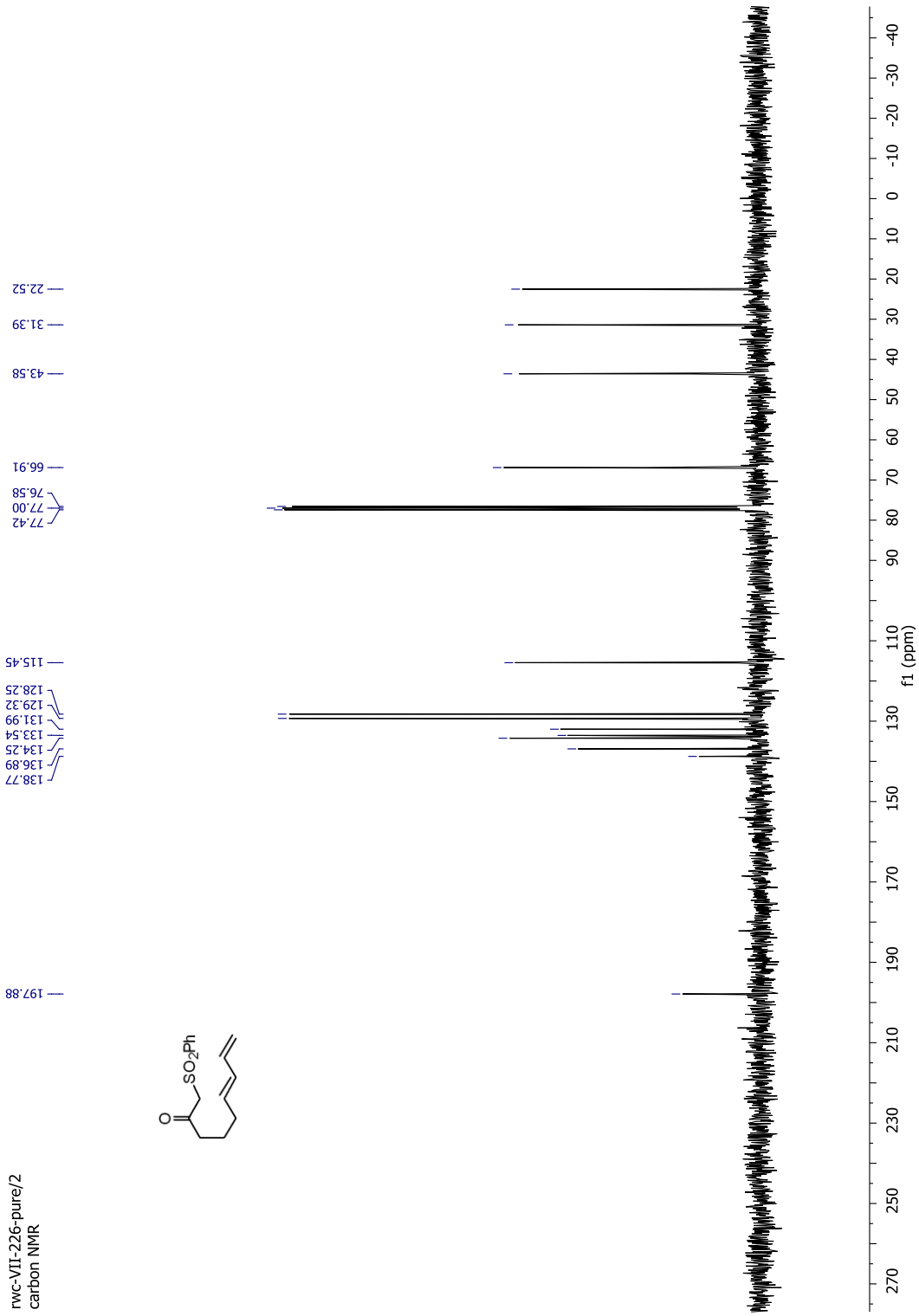
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77.00
76.58
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43.58
31.39
22.52
f1 (ppm)

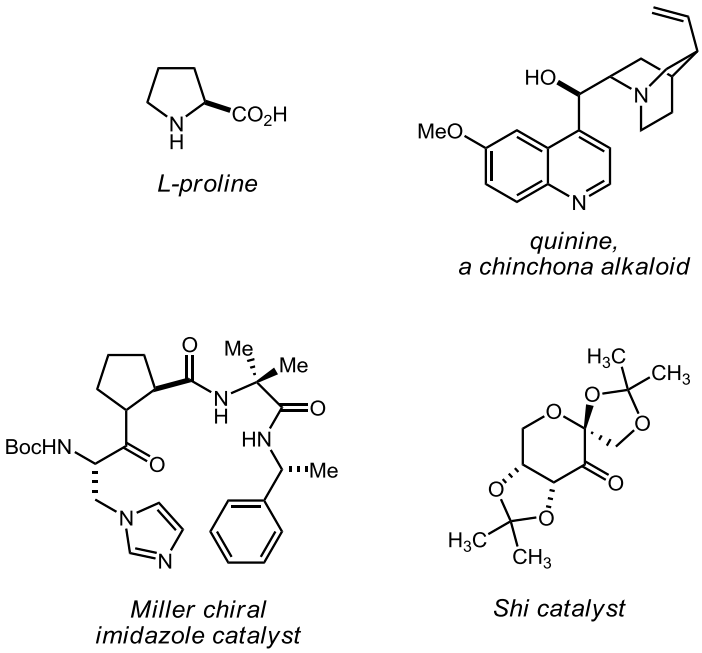
CHAPTER 3

Progress toward a New Organocatalytic Platform for Carbonyl α-Functionalization: Diastereoselective Functionalization of Fulvenes and Demonstration of the Facile Reversibility of Fulvene Formation with Electron Deficient Cyclopentadienes[1]

Introduction

Organocatalysis has increasingly become an integral and necessary tool in the synthesis of complex chiral molecules. Benefits of organocatalysis include low catalyst cost, low toxicity, and no transition metal waste. Of particular benefit, however, is the ease at which chiral organocatalysts can be derived from naturally occurring organic compounds. Indeed, some organocatalysts need no or minimal modification to effect highly enantioselective organic reactions. Some examples include proline[2] and the cinchona alkaloids[3] – both naturally existing compounds – and Miller's chiral imidazole catalysts[4] and Shi's epoxidation catalyst[5] – derived from naturally occurring amino acids and sugars, respectively.

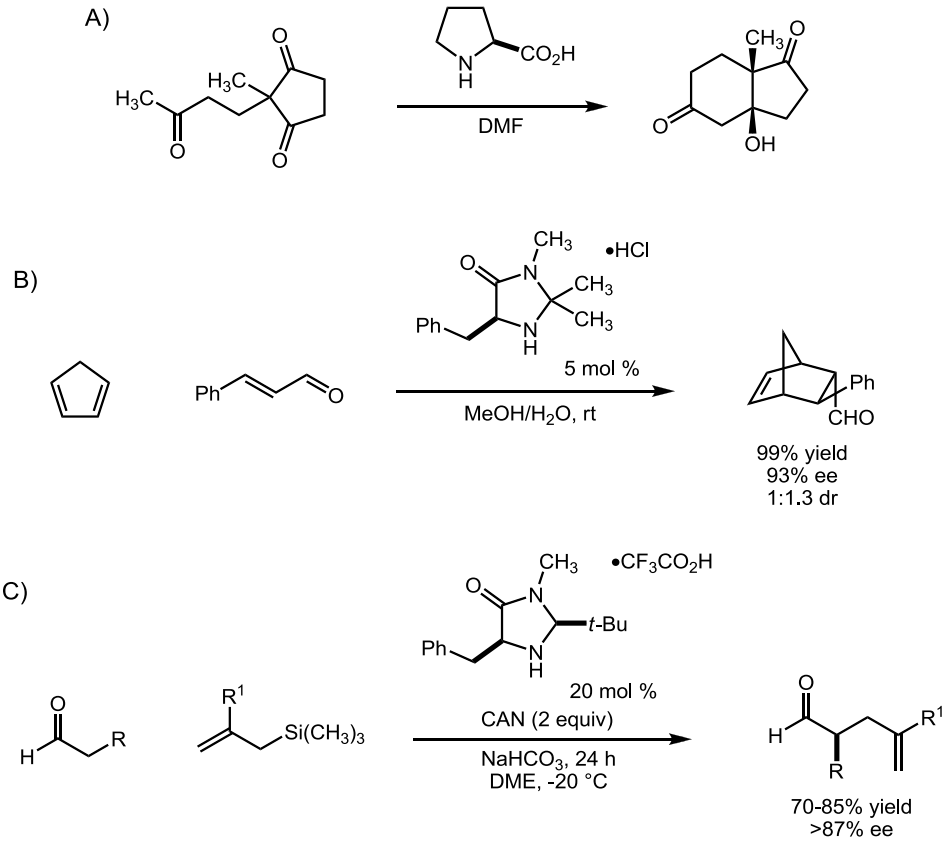
Figure 1. A) Liebig's hydration of dicyan – the first reported organocatalytic reaction, and B) several examples of common organocatalysts.



Asymmetric enamine and iminium covalent catalysis, in particular, has been especially exciting. The Hajos-Parrish reaction, as one example, in which an intramolecular aldol reaction is catalyzed by proline, was pivotal in the asymmetric synthesis of the Hajos-Parrish ketone – an important chiral intermediate in many steroid syntheses (Figure 2, A).[6] More recently, the use of imidazolidinone catalysts, derived from amino acids, have proven effective in a number of organic transformations including Michael additions, Diels-Alder cycloadditions, and many others (Figure 2, B).[7] SOMO catalysis, in which the enamine intermediate is oxidized by ceric ammonium nitrate to furnish a reactive radical cation, has allowed the methodology to move beyond traditional electrophilic reacting partners.[8] All of these reactions involve imine or enamine formation with a chiral catalyst. The catalyst then directs the

diastereoselectivity of an incoming electrophile, diene, or SOMOphile, depending on the desired reactivity. As a final part of the catalytic cycle, the catalyst must be hydrolyzed, regenerating the catalyst and furnishing the enantio-enriched carbonyl product.

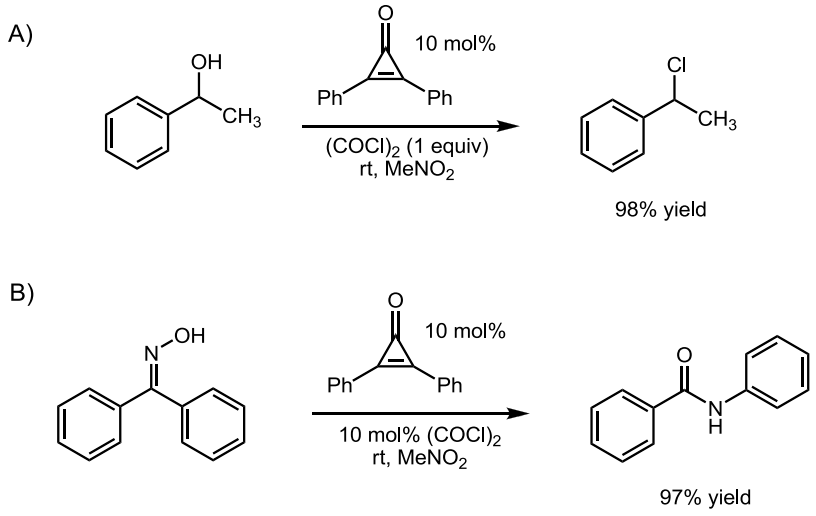
Figure 2. Several examples of enamine and iminium catalysis, A) the Hajos-Parrish reaction, B) imidazolidinone catalysis, and C) SOMO catalysis.



The Lambert group has recently initiated research into the area of aromatic molecules and ions as a new platform for organocatalysis. Rather than employing heteroatoms for the stabilization of transiently charged intermediates, the stability associated with aromaticity is exploited to effect organic transformations. A number of

transformations have already been developed by our group including catalytic Mitsunobu-like chlorination reactions and Beckmann rearrangements (Figure 3, A & B).[9] Both reactions involve the catalytic activation of hydroxyl groups by aromatic cyclopropenium ion catalysts. While these first two transformations use three-carbon containing cyclopropenes, we are also interested in the use of five-membered ring aromatic systems.

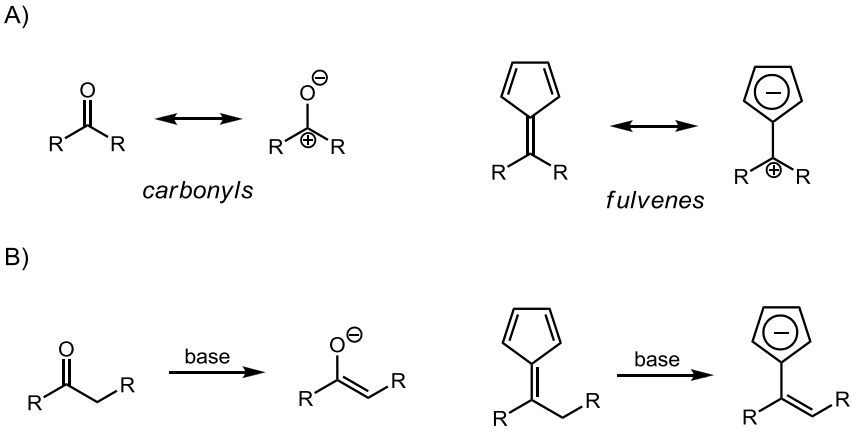
Figure 3. Examples of aromatic ion catalysis reactions developed by Lambert and coworkers, A) cyclopropenium-catalyzed chlorodehydration and B) cyclopropenium-initiated Beckmann rearrangement.



Fulvenes, we thought, could offer an interesting entry into a new organocatalytic paradigm similar to that of enamine and iminium catalysis. Fulvenes are a special class of psuedoaromatic compounds.[10] Fulvenes are similar to carbonyls in that they contain a highly polarized π-bond. In carbonyls, the polarization is the result of resonance

structures stabilized by the inherent electronegativity of the oxygen atom while in fulvenes the negative charge is stabilized by aromaticity (Figure 4, A). Similar to carbonyls and iminium ions, the 6-position of the fulvene is especially electrophilic. Fulvenes can also be deprotonated to yield so-called fulvenolates, which are nucleophilic similar to enolates and enamines (Figure 4, B).[11]

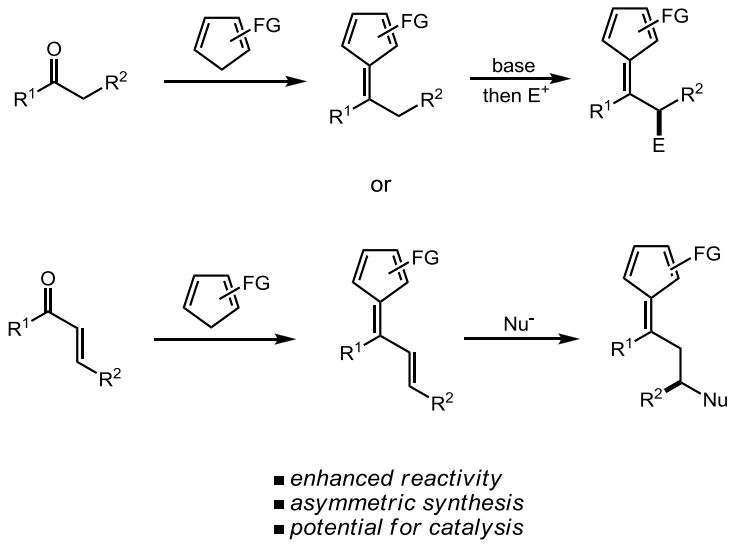
Figure 4. A) Comparison of bond polarization in carbonyls and fulvenes, and B) major contributing resonance structures of enolates and 'fulvenolates'.



Fulvenes offer several important potential benefits beyond its carbonyl-like reactivity. Like enamines and iminiums, fulvenes are easily derived from carbonyls. A number of mild and efficient methods exist for preparing fulvenes from carbonyls and cyclopentadiene. Formation of fulvenes from functionalized cyclopentadienes, then, could offer the ability to influence sterochemical and electronic reactivity at the α- and β-positions of the carbonyl precursors (Figure 5). Appending sterically bulky chiral substituents, for example, could direct the approach of reactive electrophiles and nucleophiles, resulting in stereoselective functionalization. Electron donating and

withdrawing groups, meanwhile, would allow for the enhancement of reactivity at these positions. These electronic modifications could also be used to facilitate formation of fulvenes from carbonyls and cleavage of fulvenes back to the constituent carbonyls. It was these potential advantages that attracted our attention in the study of cyclopentadienes and fulvenes as a platform for catalysis.

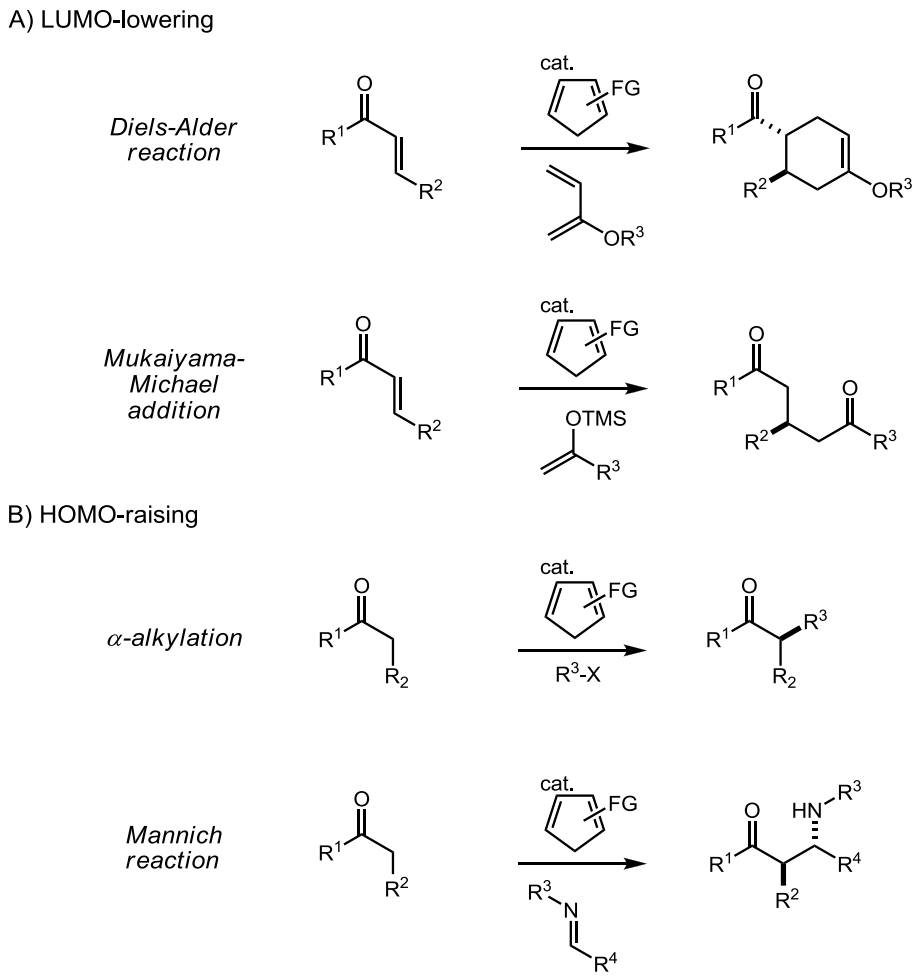
Figure 5. Potential benefits of fulvene-mediated functionalization of carbonyl containing compounds.



Proposed Fulvene Catalysis

Given the favorable reactivity of the fulvene structures and the tunability substitution would provide, we set out to investigate a potential fulvene/cyclopentadiene organocatalytic paradigm for the asymmetric functionalization of carbonyl containing compounds. Fulvene catalysis could be applied to a number of potential reactions in both LUMO-lowering and HOMO-raising activation reactions (Figure 6). LUMO-lowering reactions include functionalization of α,β-unsaturated carbonyl species. Representative examples include cycloadditions like the Diels-Alder reaction, epoxidation reactions, and conjugate additions. HOMO-raising reactions include α-alkylations, α-oxidations, and α-chlorinations, and also include aldol and Mannich reactions.

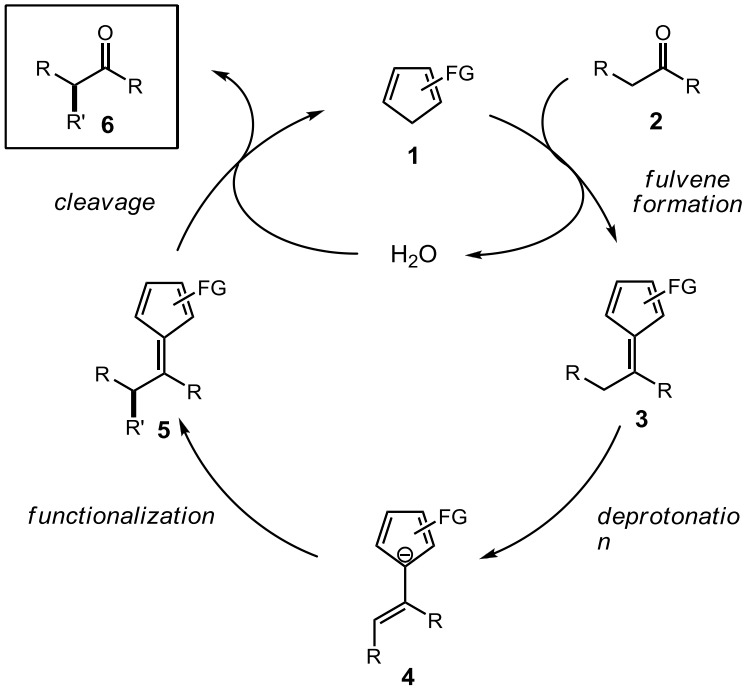
Figure 6. Potential reaction scope of asymmetric fulvene organocatalytic paradigm in A) LUMO-lowering activation and B) HOMO-raising activation reactions.



We first sought to investigate the HOMO-raising fulvene organocatalytic paradigm. In the catalytic cycle, fulvene **3** is first formed by a dehydrative addition of cyclopentadiene **1** to carbonyl substrate **2** (Figure 7). Under the reaction conditions, the fulvene is deprotonated to expose fulvenolate intermediate **4**. This fulvenolate is then intercepted by an appropriate electrophile to furnish substituted fulvene **5**. Chiral substitution on the fulvene would allow for the introduction of the electrophile in a

stereoselective manner. Finally, the fulvene would be cleaved upon addition of water, reforming cyclopentadiene **1** and furnishing the desired α-functionalized carbonyl product **6**. Whereas enamine and iminium catalysis have cationic catalytic cycles, the proposed fulvene-based catalytic cycle would be anionic, offering an interesting an valuable addition to existing methods.

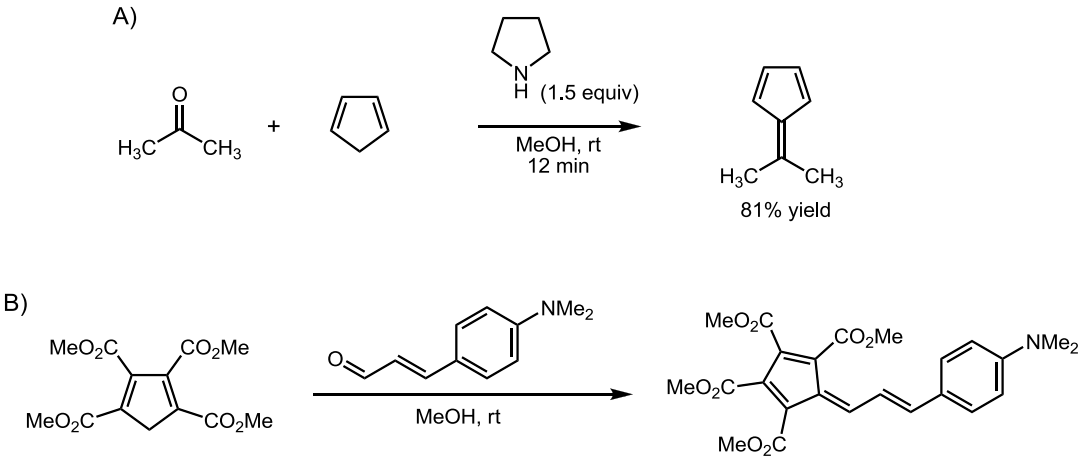
Figure 7. Proposed organocatalytic cycle for the α-functionalization of carbonyl containing compounds via fulvene catalysis.



Several steps of the observed catalytic cycle had already been reasonably well investigated in the scientific literature. Fulvene formation, for example, could be effected cleanly in the presence of a number of reagents including diethylamine[12] and metal alkoxides[13]. Perhaps the most general and mild approach was reported by Stone and

Little in which fulvenes are rapidly formed from the corresponding aldehydes or ketones and cyclopentadiene in the prepsence of pyrrolidine (Figure 8).[14] While these approaches may be amenable to our envisioned catalytic protocol, we were also interested in how substitution on the cyclopentadiene ring could impact the facility in which fulvenes are formed. Investigations by Aqad and coworkers suggest that highly acidic cyclopentadienes could form fulvenes spontaneously with carbonyls in methanol at room temperature in the absence of base.[15] Ideally, our catalyst system would feature cyclopentadienes with similar reactivity towards carbonyls.

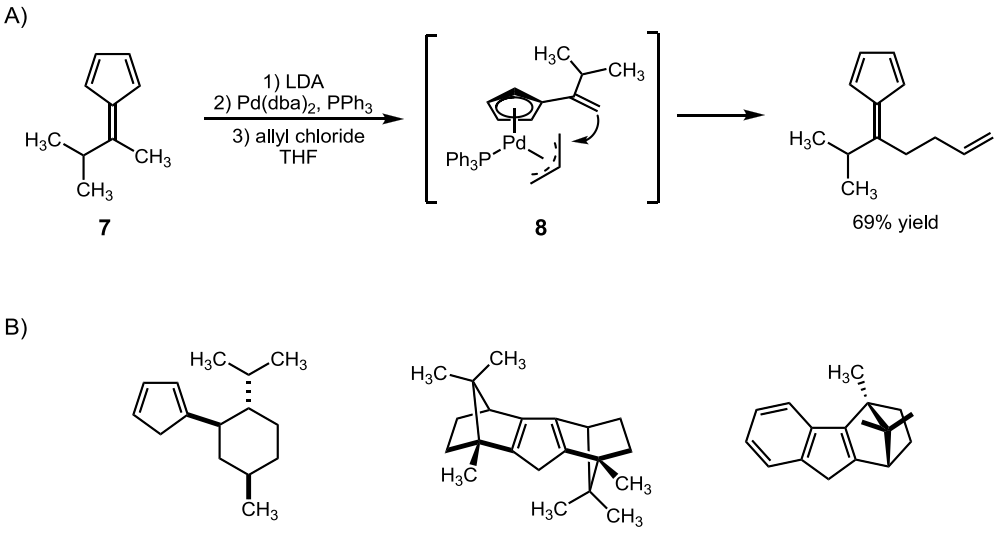
Figure 8. A) Mild fulvene formation conditions developed by Stone and Little employing pyrrolidine, and B) fulvene formation from electron deficient cyclopentadienes in the absence of base.



Deprotonation and functionalization have also been reported in the literature, albeit with some issues of regioselectivity.[16] Treatment of isobutyraldehyde derived fulvene **7** with LDA and allyl chloride in the presence of $Pd(PPh_3)_4$ led to exclusive

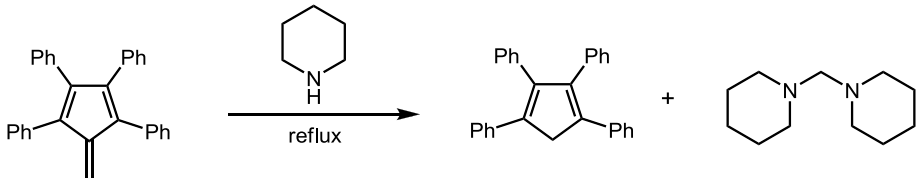
allylation at the 7-position of the fulvene substrate (Figure 9, A). The authors suggest that cyclopentadienyl-allylpalladium intermediate **8** is responsible for the high level of regioselectivity. While the use of metals represents a legitimate possibility in our catalytic scheme to effect the proper regioselectivity, we were also interested in the possibility of using substitution to properly direct functionalization. Employing sufficiently bulky groups along the ring should disfavor substitution on the ring while substitution with electron withdrawing groups could potentially make the deprotonation more facile. In addition, we were also interested in the possibility that chiral substitutents could direct stereospecificity in addition to disfavoring ring alkylation. A number of chiral cyclopentadienes and indenes derived from naturally occurring chiral compounds had already been described and we were interested in investigating several more (Figure 9, B).[17]

Figure 9. A) Regioselective palladium-catalyzed fulvene allylation reaction developed by Söderberg and coworkers, and B) examples of chiral substituted cyclopentadienes and indenes.



Cleavage, however, is by far the most understudied of the components of our fulvene-promoted catalytic cycle. To date, only one example of a fulvene cleavage has been reported in the literature (Figure 10).[18] Taber and coworkers discovered that upon treatment of tetraphenylfulvene with excess piperidine at elevated temperatures, tetraphenylcyclopentadiene and dipiperidylmethane were isolated. The failure of fulvenes to readily undergo cleavage is likely the result of poor stabilization of the negative charge by the cyclopentadienyl aromatic system. Increasing the stabilization of negative charge by introducing electron withdrawing groups to the cyclopentadiene structure, we reasoned, may increase the reversibility of fulvene formation.

Figure 10. Only known cleavage of a fulvene.



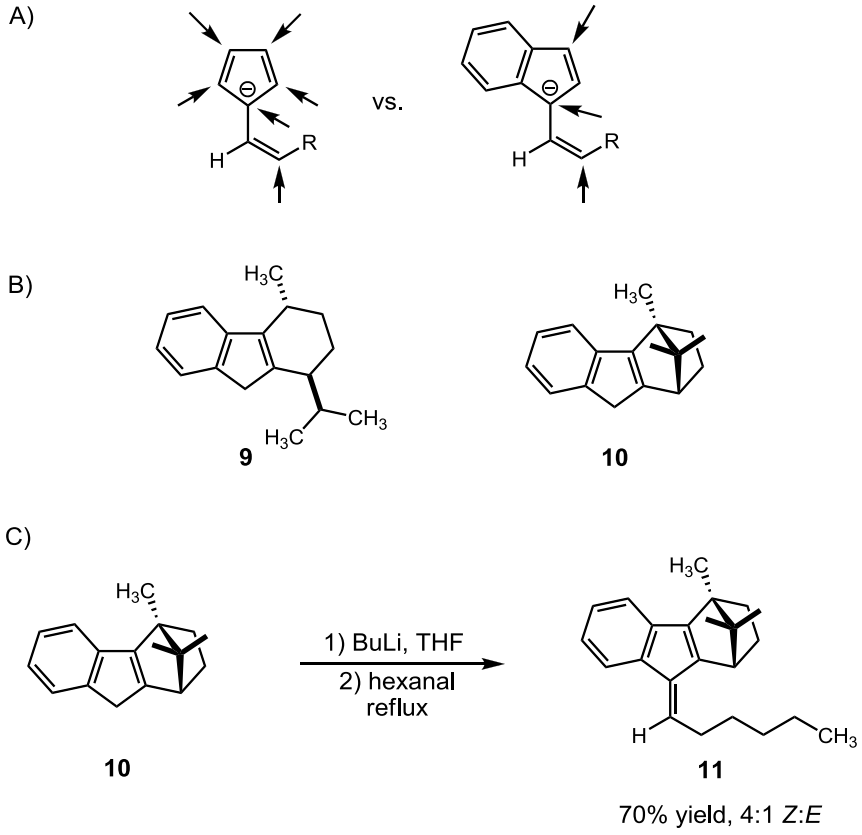
We therefore initiated an investigation into both the asymmetric α-functionalization and the cleavage of activated fulvene substrates. Asymmetric α-functionalization would be effected by adding chiral substitutents to the cyclopentadiene precursor to fulvenes. These chiral substituents would direct the facial selectivity of the addition of electrophiles. Cleavage of fulvenes back to their constituent carbonyl and cyclopentadienes would be pursued by the addition of electron withdrawing groups to the cyclopentadiene structure. The confluence of the successful α-activation and cleavage of

fulvenes with the already established mild fulvene formation would then lead to a realization of an asymmetric fulvene-based organocatalytic system.

Results and Discussion

Our efforts to realize a fulvene catalyzed α-functionalization began with investigations of the asymmetric alkylation of indenyl derived fulvene substrates. Indenyl fulvenes, we thought, were an ideal starting point for functionalization as three of the five positions along the fulvenolate ring were unlikely to react because nonaromatic products would result (Figure 11, A). Furthermore, a number of chiral indenes had previously been reported in the literature (Figure 11, B).[19] Chiral indene **9**, derived from carvone, failed to undergo the requisite fulvenation reaction with a number of aldehydes and under a number of different reaction conditions. The camphor-derived chiral indene **10**, however, underwent relatively clean conversion to fulvene **11** upon treatment with butyl lithium and hexanal (Figure 11, C). Geometry of the formed alkene was approximately 4:1 in favor of the product shown as the *E* isomer results in unfavorable interactions between the alkyl chain and planar aryl hydrogen.

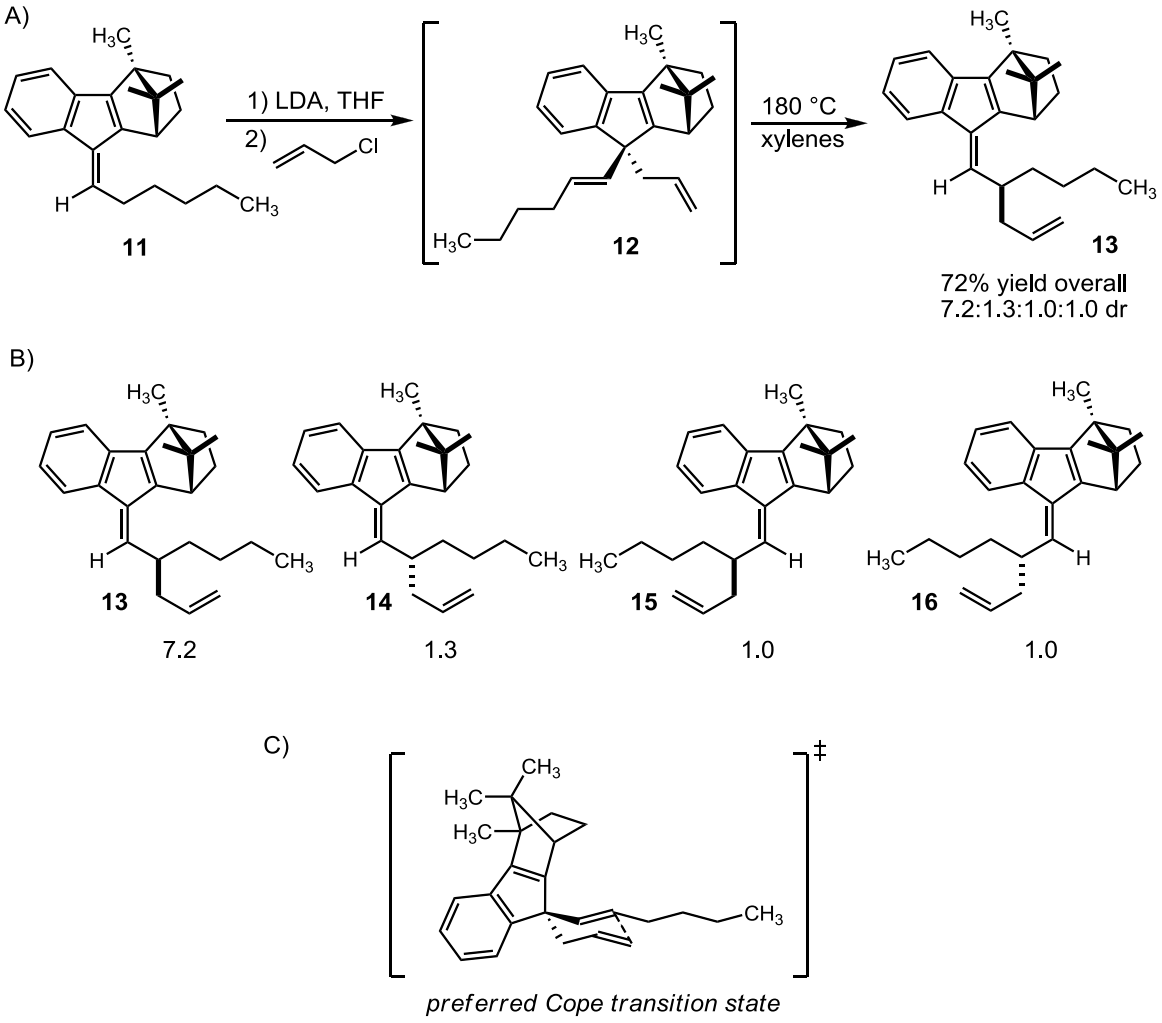
Figure 11. A) Electrophilic functionalization sites of cyclopentadienyl fulvenes versus indenyl fulvenes, B) examples of previously reported chiral indenes derived from chiral pool precursors, and C) formation of a fulvene from chiral indene precursor.



We next sought to investigate the alkylation of the chiral indenyl fulvene substrate. Upon treatment with lithium diisopropylamide, followed by allyl chloride, a mixture of allylated compounds consisting primarily of compound **12** (Figure 12, A). While none of the desired α-allylated product was found, we realized that the ring-allylated product could be isomerized to the desired product via a Cope rearrangement. The reaction would be driven forward by the more stable pseudo-aromatic fulvene product as well as by alkene substitution stabilization. In line with the hypothesis, a

mixture of α-allylated fulvene products were isolated in quantitative yield upon heating of **12**. Analysis of the product mixture revealed a total of four distinct stereoisomers in approximately a 7.2:1.3:1.0:1.0 ratio, with fulvene **13** as the major product (Figure 12, B). Synthesis of the enantiomerically pure allylated fulvene via the pure allylated hexanal lead to unambiguous assignment of the four diastereomers. Fulvenes **13** and **15** resulted initial allylation of the α face, whereas **14** and **16** resulted from allylation of the hindered β face. As was seen in the formation of the simple hexanal fulvene, the *Z*-stereoisomer is preferred due to minimization of steric interaction of the alkyl chain with the planar hydrogen of the aryl ring.

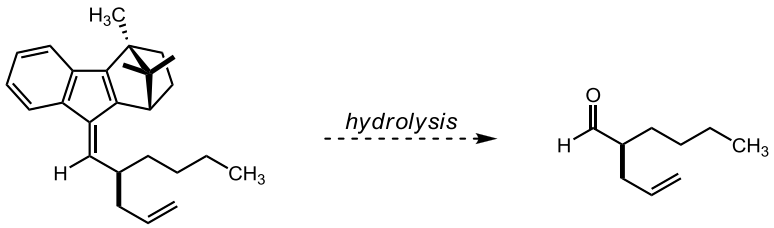
Figure 12. A) Allylation of chiral fulvene substrate and subsequent Cope rearrangement to furnish α-allylated products, B) distribution of stereoisomers of α-allylated products, and C) preferred transition state of Cope rearrangement.



Should cleavage back to the aldehyde occur, the diastereoselectivity of the previous reaction represents an enantiomeric excess of 56% (Figure 13). As such, we turned to the investigation of cleavage conditions of the indenyl fulvenes. Unfortunately, all conditions used to effect cleavage of the resultant fulvene failed to result in recovery

of the carbonyl species. These conditions included acid catalyzed hydrolysis, treatment by hydroxide bases, amine nucleophiles, hydroxylamine and phenylhydrazine. While we were extremely pleased with the potential enantiomeric excess, we realized utility of the reaction would only be realized if hydrolysis of the fulvene could be achieved.

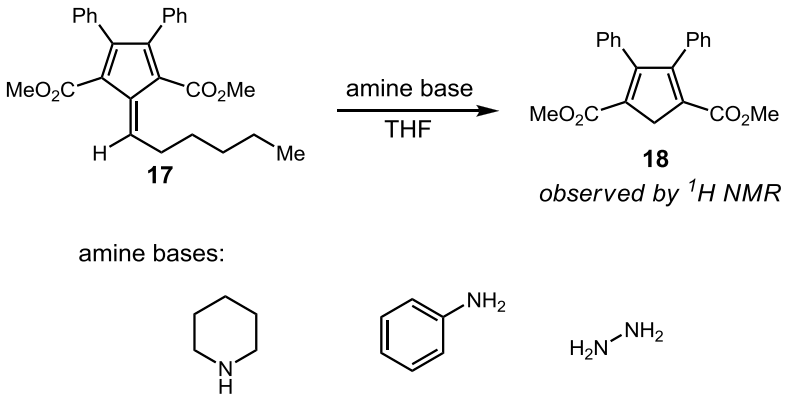
Figure 13. Potential hydrolysis of α-allylated indenyl fulvene to furnish enantioenriched aldehyde products.



With proof-of-concept of an asymmetric allylation reaction using chiral fulvenes, we next set out to show reversibility in the formation and cleavage of fulvenes from their starting carbonyl-containing species. Given the results of Taber, we sought to investigate fulvene reversibility in cyclopentadienes that were more acidic than tetraphenylcyclopentadiene. Investigations by Webster revealed that cyano- and dicyano-substituted cyclopentadienes had pK_as of approximately 10 and 2, respectively, in water.[20] Dicyanocyclopentadiene was especially interesting as a pK_a of 2 meant these cyclopentadienes were significantly more acidic than protonated amines. This, we reasoned, would make reversibility likely as the hydrolysis of imines and enamines is well documented.

Our initial investigations involved sequentially replacing the phenyl substitution of the Taber tetraphenylcyclopentadiene with electron-withdrawing groups. We soon began investigation on diphenyldiester fulvene **17**. A screen of hydrolysis conditions revealed that treatment of fulvene **17** with a range of nucleophilic amine bases at room temperature in THF led to observation of the original cyclopentadiene **18** by ^{1}H NMR (Figure 14). Furthermore, the fulvene could be formed by treatment of hexanal and pyrrolidine or aniline, suggesting reversibility was possible in the presence of the nucleophilic amine bases. The reaction mixtures, however, were complicated by a number of α-functionalization side reactions that were occurring under the reaction conditions and the terminal outcome of the hexyl chain was unclear.

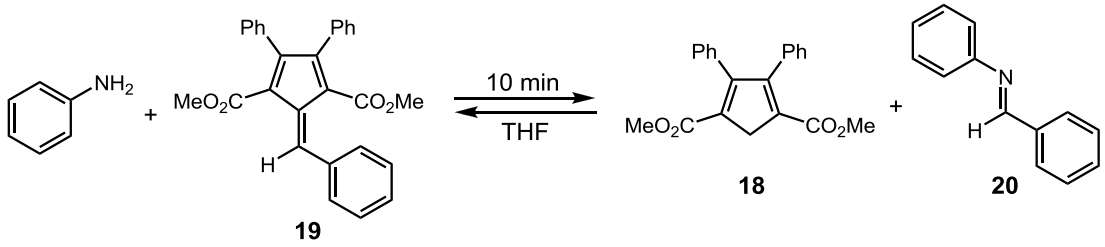
Figure 14. Demonstration of cleavage of an electron deficient fulvene by nucleophilic amine bases.



In order to probe the reversibility of the fulvene formation, we investigated the cleavage and formation of the benzaldehyde-derived fulvene. Using aniline as the nucleophilic amine base, it was discovered that fulvene **19** could be cleanly formed and

cleaved at room temperature in THF without degradation (Figure 15). The aniline-benzaldehyde Schiff base **20**, we found, was actually the reacting partner in the formation of the fulvene as this Schiff base formed more rapidly than the fulvene itself. As such, combinations of benzaldehyde-derived fulvene **19** and aniline or benzaldehyde Schiff base **20** and cyclopentadiene **18** both established a fulvene/imine ratio of approximately 7.0:1 in in less than ten minutes. This marked the discovery of the first fulvene-imine equilibrium reaction.

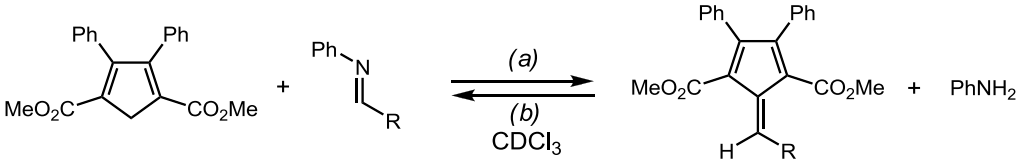
Figure 15. Demonstration of first reversible fulvenation with an electron deficient cyclopentadiene and aniline.

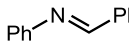
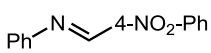
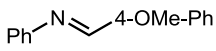
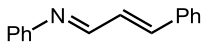
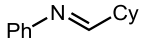


Having realized the first reversible fulvenation, we then sought to examine its scope (Table 1). It was found that after only 60 minutes in *d*-chloroform, an equilibrium ratio of ~2.3:1 fulvene/imine was formed from the cyclopentadiene and the imine derived from aniline and benzaldehyde (entry 1). As would be expected, the ratio is independent of whether starting from the the imine and cyclopentadiene or from aniline and fulvene. The use of electron withdrawing or electron donating groups largely had no effect on the equilibrium ratios, however, the presence of a methoxy group greatly slowed the time needed to reach equilibrium (entries 2 & 3). The use of an imine derived from cinnamaldehyde resulted in slow conversion to an equilibrium greatly favoring the

fulvene (entry 4). We attribute this occurrence to less unfavorable steric interaction between the cyclopentadiene and the styrenyl group compared to that of simple benzaldehyde derived substrates. Aliphatic aldehyde derived fulvenes established an equilibrium much faster than the aryl substrates (entry 5). Slow decomposition of the substrate, however, led to inconsistent results in terms of the exact ratio of fulvene to imine.

Table 1. Scope of reversible fulvenation with various fulvenyl substrates.[a]



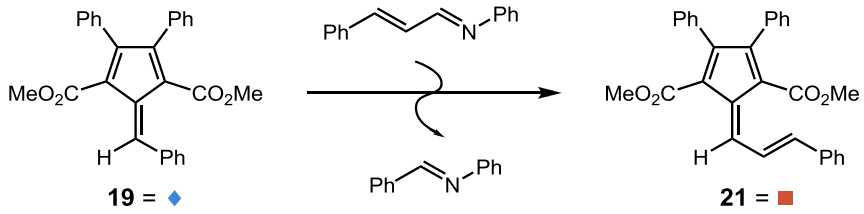
entry	imine	time	F:I *(a)*	F:I *(b)*
1		60 m	2.2:1	2.5:1
2		120 m	3.1:1	2.4:1
3		20 h	2.7:1	2.2:1
4		12 h	>20:1	>20:1
5		10 m	13.1:1	6.3:1

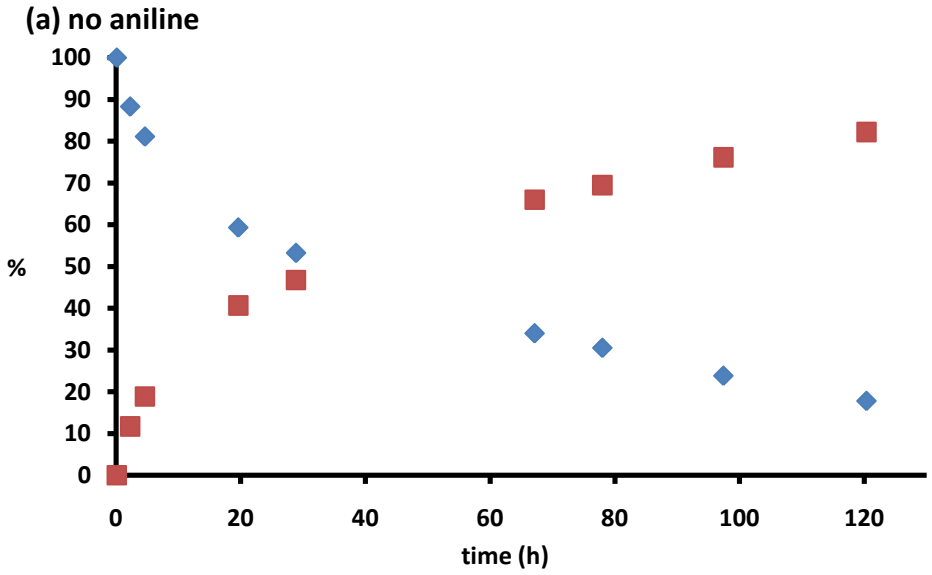
[a] Fulvene and imine ratios were determined by ^{1}H NMR relative to Bn_2O as an internal standard.

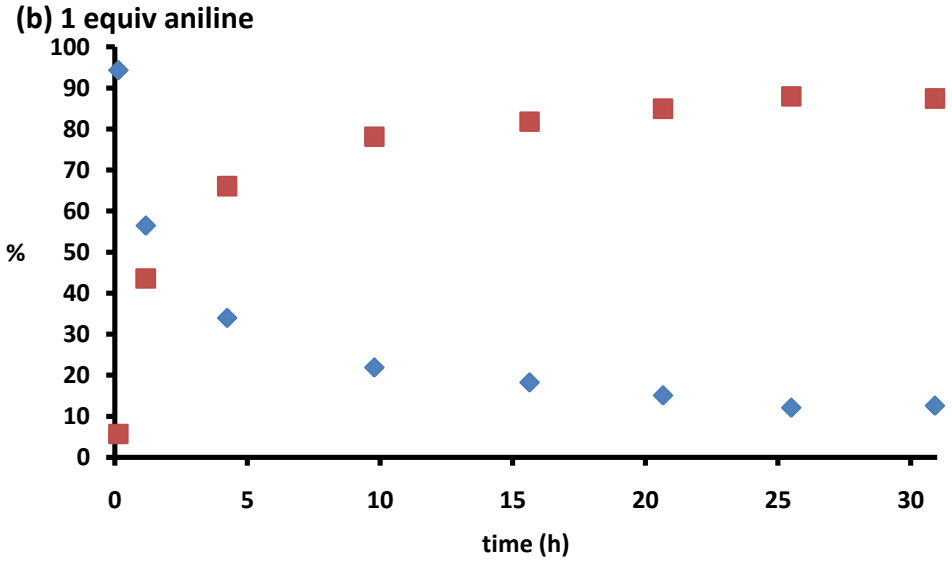
Under a potential catalytic system, the cyclopentadienyl unit of the fulvene would have to be transferrable from imine product to imine substrate *in situ*. Furthermore, the rate of the transfer should be sufficiently fast in order to be a viable catalytic platform. To probe this exchange, we exposed the benzylidene fulvene **19** to the imine derived from cinnamaldehyde and aniline and tracked concentrations of **19** and cinnamaldehyde-

derived fulvene **20** over time by ^{1}H NMR (Figure 16). It was found that exchange of the alkylidene unit indeed occurred under the reaction conditions, favoring the cinnamaldehyde-derived fulvene (Figure 16, A). The rate, however, was too slow to show the final equilibrium concentrations of the two fulvenes as concentrations continued to change after 5 days. The addition of an equivalent of aniline increased the rate of exchange considerably and an equilibrium ratio of approximately 8:1 between **19** and **21** after 25 hours (Figure 16, B).

Figure 16. Exchange experiment between phenyl- and styrenyl-substituted fulvenes.







Concluding Remarks

In conclusion, the first diastereoselective α-functionalization of chiral fulvenes has been demonstrated. Allylation and subsequent Cope-rearrangement of the camphor derived fulvene led to an enriched distribution of stereoisomeric products. Although hydrolysis of this product to its constituent cyclopentadiene and aldehyde would result in a 56% ee for the auxiliary, conditions for such a reaction have not been realized.

Reversible fulvenation has also been demonstrated. Using an electron deficient diphenyl-diestercyclopentadiene, both formation and cleavage of the derived-fulvenes was executed upon treatment with aniline. Electron deficient and electron rich substrates and vinylogous aryl substrates were investigated. Electronics appear to have little influence on the final ratio of fulvene to imine, however, the rate is significantly impeded by the presence of electron donating groups. Fulvene to imine ratio was significantly in favor of fulvene in the case of the cinnamyl derived substrates, leading to the suggestion that sterics may be the primary predictor of final product ratios.

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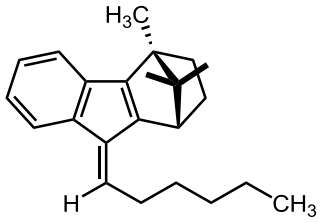
Supporting Information

General Information:

All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred by syringe under argon. Organic solutions were concentrated using a Buchi rotary evaporator. Diethyl ether, tetrahydrofuran, and methylene chloride (CH_2Cl_2) were dried using a J.C. Meyer solvent purification system. Triethylamine (Et_3N), aniline, cyclohexylamine and n-butylamine were freshly distilled over CaH_2 under argon. All other commercial reagents were used as provided. Flash column chromatography was performed employing 32-63 μm silica gel (Dynamic Adsorbents Inc). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (EMD).

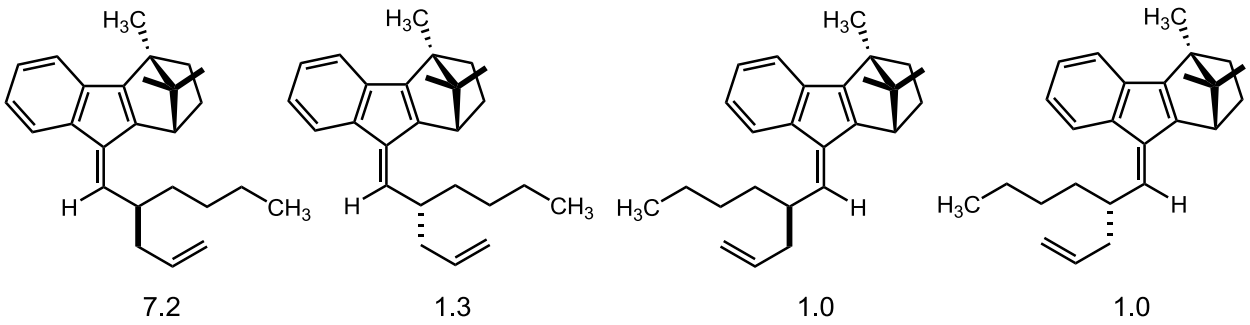
^1H and ^{13}C NMR were recorded in $CDCl_3$ on Bruker DRX-300, DRX-400, and DRX-500 spectrometers as noted. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet Avatar 370 DTGS (Thermo) using NaCl salt plates. High-resolution mass spectra were obtained from the Columbia University Mass Spectrometery Facility on JOEL JMS-HX110 HF mass spectrometer using the indicated ionization mode.

Experimental Procedures:



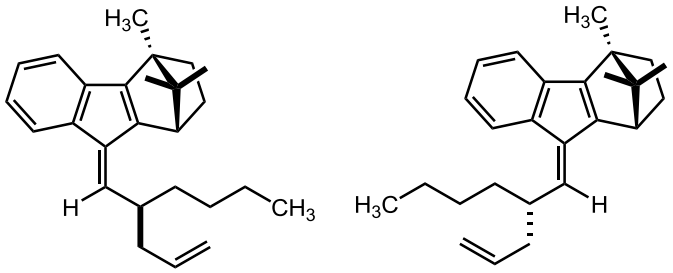
Hexanal-derived fulvene of camphor-derived indene: Camphor-derived indene (213 mg, 0.95 mmol) was dissolved in THF (1 mL) in a vial and cooled to 0 °C. Butyl lithium (2.5M in hexanes, 0.43 mL, 1.04 mmol) was then added dropwise with stirring. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Hexanal (234 μL, 1.90 mmol) was added dropwise and then the vial was capped and heated to 65 °C for 4 h. The reaction mixture was allowed to cool to room temperature and saturated aqueous NH_4Cl solution (2 mL) was added. The biphasic solution was extracted with ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparatory TLC (100% hexanes) furnished the pure fulvene as a light yellow oil (210 mg, 0.685 mmol, 72% yield, 4:1 *Z*/*E*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9 Hz, 1H (minor), Ar**H**), 7.48 (d, *J* = 9 Hz, 1H (major), Ar**H**), 7.24–7.01 (m, 3H, Ar**H**), 6.46 (t, *J* = 9 Hz, 1H (major), C=C**H**CH_2), 6.12 (t, *J* = 9 Hz, 1H (minor), C=C**H**CH_2), 2.92 (d, *J* = 3 Hz, 1H (major), C**H**), 2.75 (q, *J* = 9 Hz, 1H (minor), C=CHC$\mathbf{H_2}$), 2.71 (d, *J* = 3 Hz, 1H (minor), C**H**), 2.58 (q, *J* = 9 Hz, 1H (major), C=CHC$\mathbf{H_2}$), 2.10–1.92 (m, 1H, aliphatic), 1.84–1.71 (m, 1H, aliphatic), 1.66–1.49 (m, 1H, aliphatic), 1.45 – 1.31 (m, 7H, aliphatic), 1.28–1.00 (m, 3H, aliphatic), 0.97–0.84 (m, 9H, aliphatic); ^{13}C NMR (100 MHz, $CDCl_3$) 154.4, 145.7, 140.9, 138.1, 135.0, 133.3, 129.6, 126.7, 126.4, 126.0, 124.1, 123.4, 123.3, 118.9, 118.0,

117.8, 67.9, 60.4, 52.7, 52.4, 49.1, 32.9, 31.5, 29.7, 29.5, 29.4, 26.4, 26.2, 25.6, 22.5, 20.2, 19.3, 14.0, 12.1, 12.0.



α-Allylated camphor indenyl fulvene: Diisopropylamine (55 μL, 0.39 mmol) was dissolved in THF (2 mL) and the solution was cooled to -78 °C. Butyl lithium (2.5 M in hexanes, 150 μL, 0.36 mmol) was then added dropwise with stirring. The reaction mixture was warmed to room temperature and stirred for 10 min. The mixture was cooled back to -78 °C and a solution of fulvene (0.100 g, 0.33 mmol) in THF (2 mL) was added. The reaction mixture was warmed to room temperature for 10 min then recooled to -78 °C. Allyl chloride (29 μL, 0.36 mmol) was added. The reaction mixture was then stirred at -78 °C for 30 min, allowed to warm to room temperature, then stirred for an additional 6 h. Saturated aqueous NH_4Cl (5 mL) was added. The biphasic solution was extracted with ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparatory TLC (100% hexanes) furnished the allylated compound as a light yellow oil (71 mg, 0.205 mmol, 63% yield) as a mixture of isomers.

The mixture of allylated fulvenes isomers (71 mg, 0.205 mmol) were dissolved in xylenes (8 mL) in a high pressure glass tube and the solution was sparged with argon for 15 min. The tube was sealed and heated to 150 °C for 18 h. The solvent was removed to furnish the title compound (0.71 mg, 0.205 mmol, 100% yield, 7.2:1.3:1.0:1.0 mixture of isomers)[1] as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 9 Hz, 1H (minor), Ar**H**), 7.49 (d, J = 9 Hz, 1H (major), Ar**H**), 7.24–7.01 (m, 3H, Ar**H**), 6.16 (d, J = 9 Hz, 1H (major), C=C**H**CH), 5.87 (t, J = 9 Hz, 1H (minor), C=C**H**CH), 5.83–5.66 (m, 1H, C**H**=CH_2), 5.07–4.89 (m, 2H, C**H**=CH_2), 3.00–2.41 (m, 2H, allylic), 2.38–2.10 (m, 2H, allylic), 2.10–1.92 (m, 1H, aliphatic), 1.84–1.71 (m, 1H, aliphatic), 1.66–1.49 (m, 1H, aliphatic), 1.45 – 1.31 (m, 7H, aliphatic), 1.28–1.00 (m, 3H, aliphatic), 0.97–0.84 (m, 9H, aliphatic).

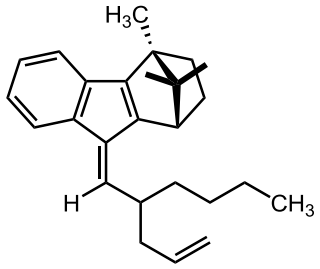


3.7 1.0

α-Allylated camphor indenyl fulvene prepared from enantioenriched aldehyde: Camphor-derived indene (120 mg, 0.535 mmol) was dissolved in THF (0.5 mL) in a vial and cooled to 0 °C. Butyl lithium (2.5M in hexanes, 0.235 mL, 0.589 mmol) was then added dropwise with stirring. The reaction mixture was allowed to warm to room

[1] Identity and ratios of isomers were determined by a combination of NOE, and GC and by comparing the products to independently prepared enantioenriched and racemic products.

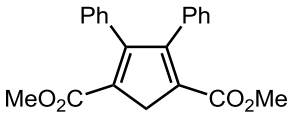
temperature and stirred for 30 min. (*S*)-2-Allylhexanal[2] (100 mg, 0.535 mmol) was added dropwise and then the reaction mixture was stirred for 18 h. Saturated aqueous NH_4Cl solution (2 mL) was added. The biphasic solution was extracted with ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparatory TLC (100% hexanes) furnished a 1:1 mixture of the fulvene (3.7:1, *E*/*Z*) and starting material as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9 Hz, 1H (minor), Ar**H**), 7.49 (d, *J* = 9 Hz, 1H (major), Ar**H**), 7.24–7.01 (m, 3H, Ar**H**), 6.16 (d, *J* = 9 Hz, 1H (major), C=C**H**CH), 5.87 (t, *J* = 9 Hz, 1H (minor), C=C**H**CH), 5.83–5.66 (m, 1H, C**H**=CH_2), 5.07–4.89 (m, 2H, C**H**=CH_2), 3.00–2.41 (m, 2H, allylic), 2.38–2.10 (m, 2H, allylic), 2.10–1.92 (m, 1H, aliphatic), 1.84–1.71 (m, 1H, aliphatic), 1.66–1.49 (m, 1H, aliphatic), 1.45 – 1.31 (m, 7H, aliphatic), 1.28–1.00 (m, 3H, aliphatic), 0.97–0.84 (m, 9H, aliphatic).[3]



α-Allylated camphor indenyl fulvene prepared from racemic aldehyde: Camphor-derived indene (120 mg, 0.535 mmol) was dissolved in THF (0.5 mL) in a vial and cooled to 0 °C. Butyl lithium (2.5M in hexanes, 0.235 mL, 0.589 mmol) was then added dropwise with stirring. The reaction mixture was allowed to warm to room temperature

[2] Prepared via Myer's alkylation: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
[3] Starting material peaks have been excluded for clarity.

and stirred for 30 min. (±)-2-Allylhexanal[4] (100 mg, 0.535 mmol) was added dropwise and then the reaction mixture was stirred for 18 h. Saturated aqueous NH_4Cl solution (2 mL) was added. The biphasic solution was extracted with ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparatory TLC (100% hexanes) furnished a 2:1 mixture of the fulvene (3.7:1, *E*/*Z*) and starting material as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9 Hz, 1H (minor), Ar**H**), 7.49 (d, *J* = 9 Hz, 1H (major), Ar**H**), 7.24–7.01 (m, 3H, Ar**H**), 6.16 (d, *J* = 9 Hz, 1H (major), C=C**H**CH), 5.87 (t, *J* = 9 Hz, 1H (minor), C=C**H**CH), 5.83–5.66 (m, 1H, C**H**=CH_2), 5.07–4.89 (m, 2H, C**H**=CH_2), 3.00–2.41 (m, 2H, allylic), 2.38–2.10 (m, 2H, allylic), 2.10–1.92 (m, 1H, aliphatic), 1.84–1.71 (m, 1H, aliphatic), 1.66–1.49 (m, 1H, aliphatic), 1.45 – 1.31 (m, 7H, aliphatic), 1.28–1.00 (m, 3H, aliphatic), 0.97–0.84 (m, 9H, aliphatic).[5]



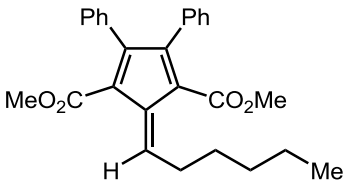
Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate: Dimethyl 2-oxo-4,5-diphenylcyclopenta-3,5-diene-1,3-dicaroxylate (5.24 g, 15.0 mmol) was dissolved in anhydrous ethanol (150 mL). The solution was cooled to 0 °C and $NaBH_4$ (0.563 g, 15.0 mmol) was added in three portions over ten minutes with vigorous stirring. The reaction mixture was allowed to continue stirring for 15 min at 0 °C and was then quenched by addition of water (100 mL). The mixture was extracted with EtOAc (250 mL) and the resulting organic layer was washed with brine (150 mL), dried with $MgSO_4$, and

[4] Cuvigny, T.; Normant, H. *Organometallics in Chemical Synthesis* **1971**, *1*, 237.
[5] Starting material peaks have been excluded for clarity.

concentrated *in vacuo*. The crude alcohol was used in the following step without further purification.

The crude alcohol was dissolved in THF (200 mL). Acetic anhydride (2.13 mL, 22.5 mmol), triethylamine (3.14 mL, 22.5 mmol), and 4-(dimethylamino)pyridine (0.183 g, 1.50 mmol) were then added and the reaction was stirred at room temperature for 2 hr. Water (150 mL) was added and the reaction was extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude acetate was then used without further purification.

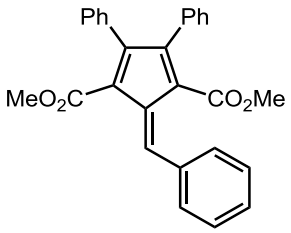
The crude acetate from the previous step was dissolved in dichloromethane (200 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (6.72 mL, 45 mmol) was added. The reaction mixture was stirred at room temperature for 2 hr and then quenched by addition of 1M aqueous HCl (100 mL). This mixture was extracted with EtOAc (200 mL × 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo.* The crude oil was purified by flash chromatography (dichloromethane) and recrystallized twice from ether to yield the title compound (2.84 g, 8.49 mmol, 57% yield from ketone) as fine colorless crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 6H, Ar**H**), 7.00 (m, 4H, Ar**H**), 3.95 (s, 2H, C$\mathbf{H_2}$), 3.68 (s, 6H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) 164.2, 156.2, 134.0, 133.8, 129.1, 127.8, 127.3, 51.4, 43.1; IR (thin film) 1716, 1489, 1434, 1361, 1207, 1102, 1083, 1003, 741, 698 cm^{-1}; HRMS (FAB$^+$) *m/z* = 334.1205 calcd for $C_{21}H_{19}O_4$ $[M]^+$, found 334.1202.



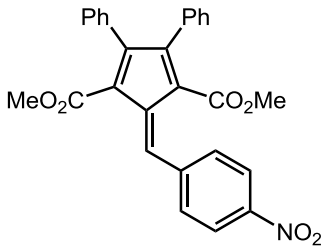
Dimethyl 2-hexylidene-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate: Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (0.050 g, 0.15 mmol) was dissolved in THF (1.5 mL). Hexanal (0.019 mL, 0.15 mmol) and pyrrolidine (0.013 mL, 0.15 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. Four drops of acetic acid were added and the mixture was diluted with EtOAc (50 mL) then washed with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL). The organic layer was then dried of $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (10% EtOAc/hexanes) to yield the title compound (37 mg, 0.088 mmol, 59% yield) as a bright yellow oil. . ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, *J* = 9 Hz, 1H, C=C**H**CH_2), 7.23–7.14 (m, 6H, Ar**H**), 7.02–6.95 (m, 4H, Ar**H**), 3.67 (s, 3H, $CO_2C\mathbf{H_3}$), 3.57 (s, 3H, $CO_2C\mathbf{H_3}$), 2.56 (q, *J* = 9 Hz, 2H, C=CHC$\mathbf{H_2}$), 1.67–1.58 (m, 2H, C$\mathbf{H_2}$), 1.42–1.33 (m, 4H, C$\mathbf{H_2}$), 0.92 (t, *J* = 9 Hz, 3H, C$\mathbf{H_3}$).

Hydrolysis experiment of dimethyl 2-hexylidene-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate: Dimethyl 2-hexylidene-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (0.05 mg, 0.01 mmol) was dissolved in THF (0.5 mL). Piperidine, aniline, or hydrazine hydrate was then added (approximately 5 drops). The reactions were allowed to stir at room temperature for 3 h. Aqeous 1M HCl solution (2 mL) was then added and the mixture was extracted with EtOAc (2 × 5mL). The combined organic layers were washed with water (5 mL), brine (5 ml), dried over $MgSO_4$ and concentrated

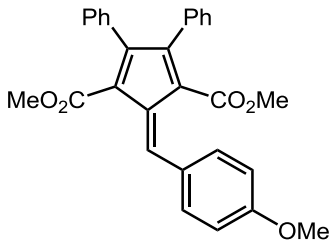
in vacuo. The crude residues were then examined by ^{1}H NMR analysis and all showed the presence of dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate.



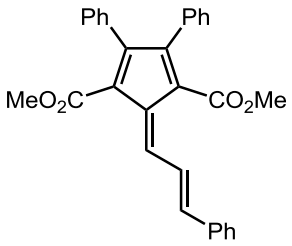
Dimethyl 2-benzylidene-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate: Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (50 mg, 0.15 mmol) was dissolved in 1 ml THF. Benzaldehyde (15 μL, 0.15 mmol) and cyclohexylamine (1.7 μL, 0.015 mmol) were added and the reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (4:1 hexanes:EtOAc) to yield the title compound (52 mg, 0.12 mmol, 80% yield) as bright yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H, Cp=C**H**-Ar), 7.40-7.50 (m, 5H, Ar**H**), 7.20 (m, 6H, Ar**H**), 7.06 (m, 4H, Ar**H**), 3.64 (s, 3H, $CO_2C\mathbf{H_3}$), 3.02 (s, 3H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 165.2, 150.7, 150.6, 145.1, 139.3, 137.0, 134.4, 133.1, 130.3, 129.6, 129.4, 129.2, 128.3, 127.8, 127.6, 127.3, 126.7, 124.5, 51.3, 51.1; IR (thin film) 2948, 1721, 1595, 1571, 1434, 1384, 1355, 1257, 1214, 1193, 1166, 1126, 1075, 1028, 997, 759, 698 cm^{-1}; HRMS (FAB^{+}) *m/z* = 422.1518 calcd for $C_{28}H_{23}O_4$ $[M]^{+}$, found 422.1524.



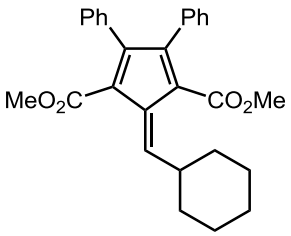
Dimethyl 2-(4-nitrobenzylidene)-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate: *N*-(4-nitrobenzylidene)aniline (68 mg, 0.30 mmol) was dissolved in THF (3 mL). Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (100 mg, 0.30 mmol) was then added and the resulting mixture was stirred at room temperature for 1 hr. Solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (4:1 hexanes:EtOAc) to yield the title compound (83 mg, 0.18 mmol, 60% yield) as a bright orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H, Cp=C**H**-Ar), 8.29 (d, *J* = 6.6 Hz, 2H, Ar**H**), 7.63 (d, *J* = 6.3 Hz, 2H, Ar**H**), 7.24 (m, 6H, Ar**H**), 7.04 (d, *J* = 5.1 Hz, 4H, Ar**H**), 3.65 (s, 3H, $CO_2C\mathbf{H_3}$), 3.09 (s, 3H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.9, 152.4, 152.1, 147.7, 143.2, 141.5, 140.9, 133.9, 132.6, 130.7, 129.3, 129.1, 128.3, 128.1, 127.5, 126.1, 124.4, 123.3, 51.4, 51.4; IR (thin film) 1721, 1592, 1520, 1435, 1383, 1345, 1258, 1215, 1193, 1165, 995, 849, 756, 699 cm^{-1}; HRMS (FAB^+) *m/z* = 467.1369 calcd for $C_{28}H_{22}NO_6$ $[M]^+$, found 467.1381.



Dimethyl 2-(4-methoxybenzylidene)-4,5-diphenylcyclopent-3,5-diene-1,3-dicarboxylate: Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (50 mg, 0.15 mmol) was dissolved in 1 ml THF. Anisaldehyde (27 μL, 0.23 mmol) and cyclohexylamine (1.7 μL, 0.015 mmol) were added and the reaction mixture was allowed to stir overnight at room temperature. Solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (4:1 hexanes:EtOAc) to furnish the title compound (40 mg, 0.088 mmol, 59% yield) as bright orange crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H, Cp=C**H**-Ar), 7.49 (d, *J* = 8.7 Hz, 2H, Ar**H**), 7.21 (m, 6H, Ar**H**), 7.07 (m, 4H, Ar**H**), 6.97 (d, *J* = 8.7 Hz, 2H, Ar**H**), 3.87 (s, 3H, $CO_2C\mathbf{H_3}$), 3.64 (s, 3H, $CO_2C\mathbf{H_3}$), 3.16 (s, 3H, $ArOC\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 165.5, 161.3 150.2, 149.7, 145.4, 137.6, 134.8, 133.5, 133.0, 132.8, 129.9, 129.7, 129.3, 129.1, 127.3, 126.5, 124.7, 114.4, 114.0, 113.7, 51.3; IR (thin film) 1719, 1590, 1509, 1433, 1356, 1306, 1255, 1165, 1085, 1027 cm^{-1}; HRMS (FAB^+) *m/z* = 452.1624 calcd for $C_{29}H_{25}O_5$ $[M]^+$, found 452.1600.



(*E*)-Dimethyl 4,5-diphenyl-2-(3-phenylallylidene) cyclopenta-3,5-diene-1,3-dicarboxylate: Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (50 mg, 0.15 mmol) was dissolved in 1 ml THF. *Trans*-cinnamaldehyde (21 μL, 0.17 mmol) and cyclohexylamine (1.7 μL, 0.015 mmol) were added and the reaction was allowed to stir overnight at room temperature. Solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (4:1 hexanes:EtOAc) to yield the title compound (44 mg, 0.098 mmol, 65% yield) as bright orange crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 12.0 Hz, 1H, Cp=C**H**-CH=CHPh), 7.68 (dd, *J* = 12.3, 15.0 Hz, 1H, Cp=CH-C**H**=CHPh), 7.56 (m, 2H, Ar**H**), 7.41 (m, 3H, Ar**H**), 7.23 (m, 7H, Cp=CH-CH=C**H**Ph + Ar**H**), 7.05 (m, 4H, Ar**H**), 3.75 (s, 3H, $CO_2C\mathbf{H_3}$), 3.64 (s, 3H, $CO_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 165.6, 149.4, 148.2, 146.4, 144.0, 137.4, 136.4, 135.0, 134.2, 130.1, 129.5, 129.2, 129.1, 128.1, 127.8, 127.7, 127.6, 127.5, 125.7, 125.4, 124.5, 52.2, 51.4; IR (thin film) 1702, 1598, 1578, 1434, 1361, 1263, 1220, 1193, 1163, 1086 cm^{-1}; HRMS (FAB^{+}) *m/z* = 448.1675 calcd for $C_{30}H_{25}O_4$ $[M]^{+}$, found 448.1693.



Dimethyl 2-(cyclohexylmethylene)-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate: Dimethyl 4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (50 mg, 0.15 mmol) was dissolved in 1 ml THF. Cyclohexanecarboxaldehyde (27 μL, 0.23 mmol) and cyclohexylamine (3.4 μL, 0.030 mmol) were added and the reaction mixture was allowed to stir overnight at room temperature. Solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (4:1 hexanes:EtOAc) to yield the title compound (49 mg, 0.11 mmol, 73% yield) as bright yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 10.8 Hz, 1H, Cp=C**H**-Cy), 7.16 (m, 6H, Ar**H**), 6.99 (m, 4H, Ar**H**), 3.69 (s, 3H, $CO_2C\mathbf{H_3}$), 3.57 (s, 3H, $CO_2C\mathbf{H_3}$), 2.63 (m, 1H, Cp=CH-C**H**R_2), 1.82 (m, 5H, C$\mathbf{H_2}$), 1.30 (m, 5H, C$\mathbf{H_2}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 165.5, 155.5, 149.4, 147.1, 137.0, 134.8, 133.7, 129.3, 129.2, 127.9, 127.8, 127.6, 127.5, 126.6, 124.2, 52.2, 51.3, 40.4, 32.7, 25.8, 25.5; IR (thin film) 2929, 2851, 1724, 1704, 1623, 1434, 1391, 1365, 1258, 1234, 1220, 1194, 1171, 1144, 1128, 994, 699 cm^{-1}; HRMS (FAB^{+}) m/z = 428.1988 calcd for $C_{28}H_{29}O_4$ $[M]^{+}$, found 428.1980.

General Procedure for Fulvene:Imine Interchange Experiments

Forward. Stock solutions (1-2 mL) of imine (0.30 M), cyclopentadiene (0.30 M) and benzyl ether (0.30 M) in $CDCl_3$ were prepared fresh. To an NMR tube, 0.20 mL of each solution was added and mixed. The fulvene:imine ratio was monitored by ^1H NMR until no change in the ratio was observed.

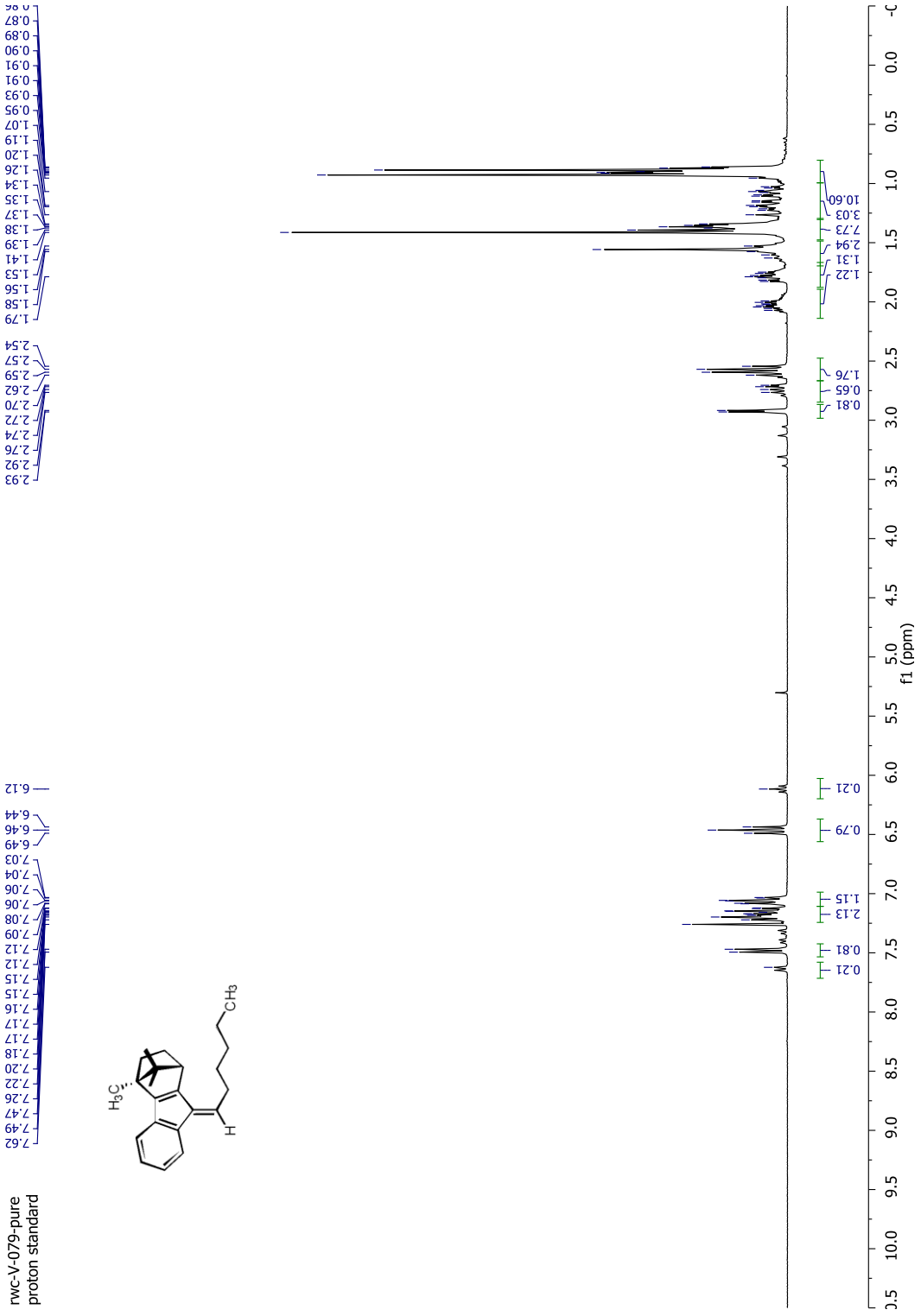
Reverse. Stock solutions (1-2 mL) of fulvene (0.30 M), amine (0.30 M) and benzyl ether (0.30 M) in $CDCl_3$ were prepared fresh. To an NMR tube, 0.20 mL of each solution was added and mixed. The fulvene:imine ratio was monitored by ^1H NMR and reported at the equilibrium time determined for the forward reaction.

Transfulvenation Experiments

No Additional Aniline. A solution of dimethyl 2-benzylidene-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (25.3 mg, 0.06 mmol) in $CDCl_3$ 300 μL was added to a solution of *N*-(3-phenylallyllidene)aniline (12.4 mg, 0.06 mmol) and benzyl ether (11.4 μL, 0.06 mmol) as internal standard in $CDCl_3$ (300 μL total volume). Reaction progress was followed by ^1H NMR over the course of five days.

Stoichiometric Aniline. A solution of dimethyl 2-benzylidene-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate (25.3 mg, 0.06 mmol) in $CDCl_3$ 300 μL was added to a solution of *N*-(3-phenylallyllidene)aniline (12.4 mg, 0.06 mmol), aniline

(5.5 μL, 0.06 mmol), and benzyl ether (11.4 μL, 0.06 mmol) as internal standard in $CDCl_3$ (300 μL total volume). Reaction progress was followed by ^1H NMR over the course of 30 hrs.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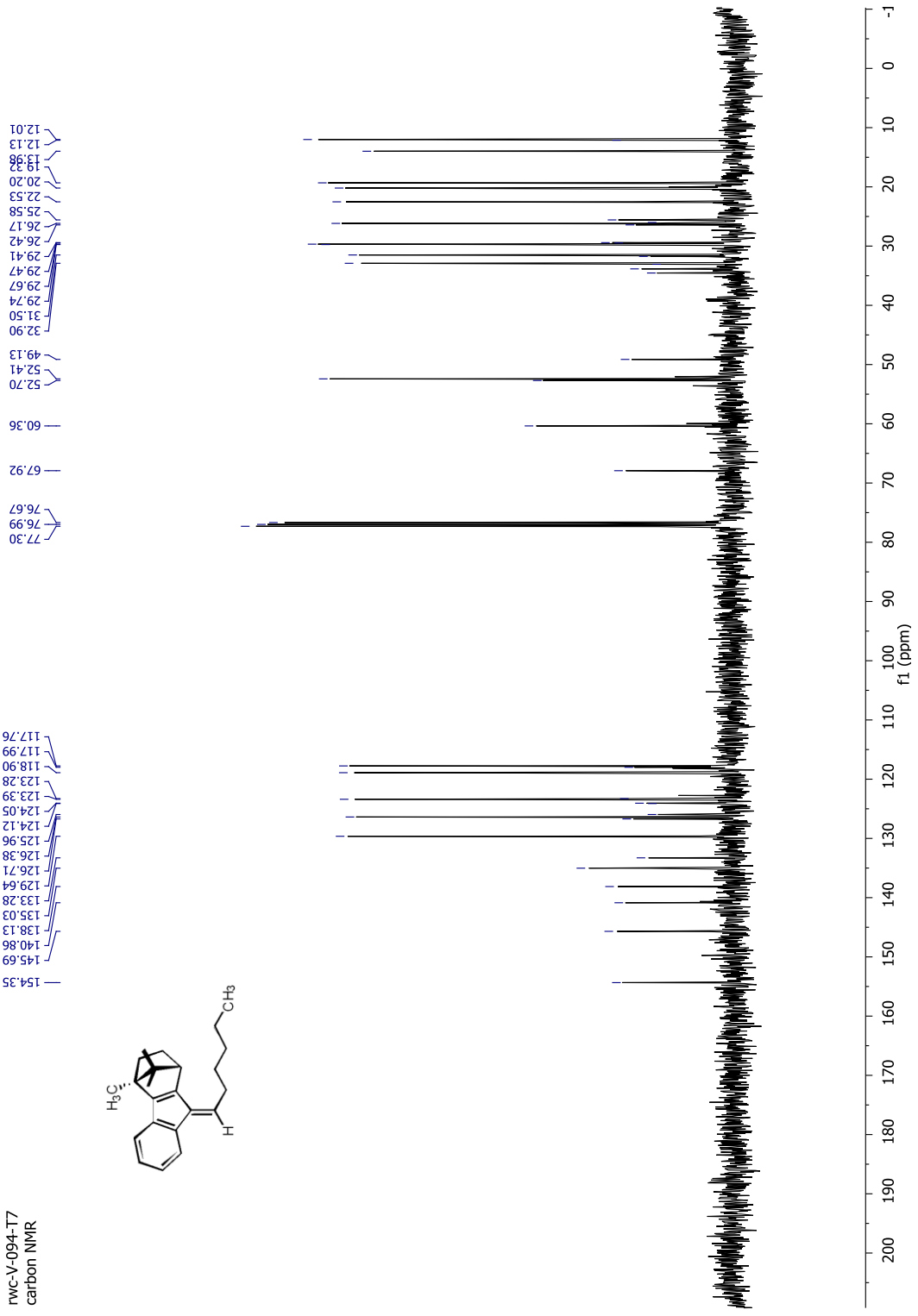
proton standard
f1 (ppm)


rwc-V-094-T7
carbon NMR
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12.13
13.98
19.32
20.20
22.53
25.58
26.17
26.42
29.41
29.47
29.67
29.74
31.50
32.90
49.13
52.41
52.70
60.36
67.92
76.67
76.99
77.30
117.76
117.99
118.90
123.28
123.39
124.05
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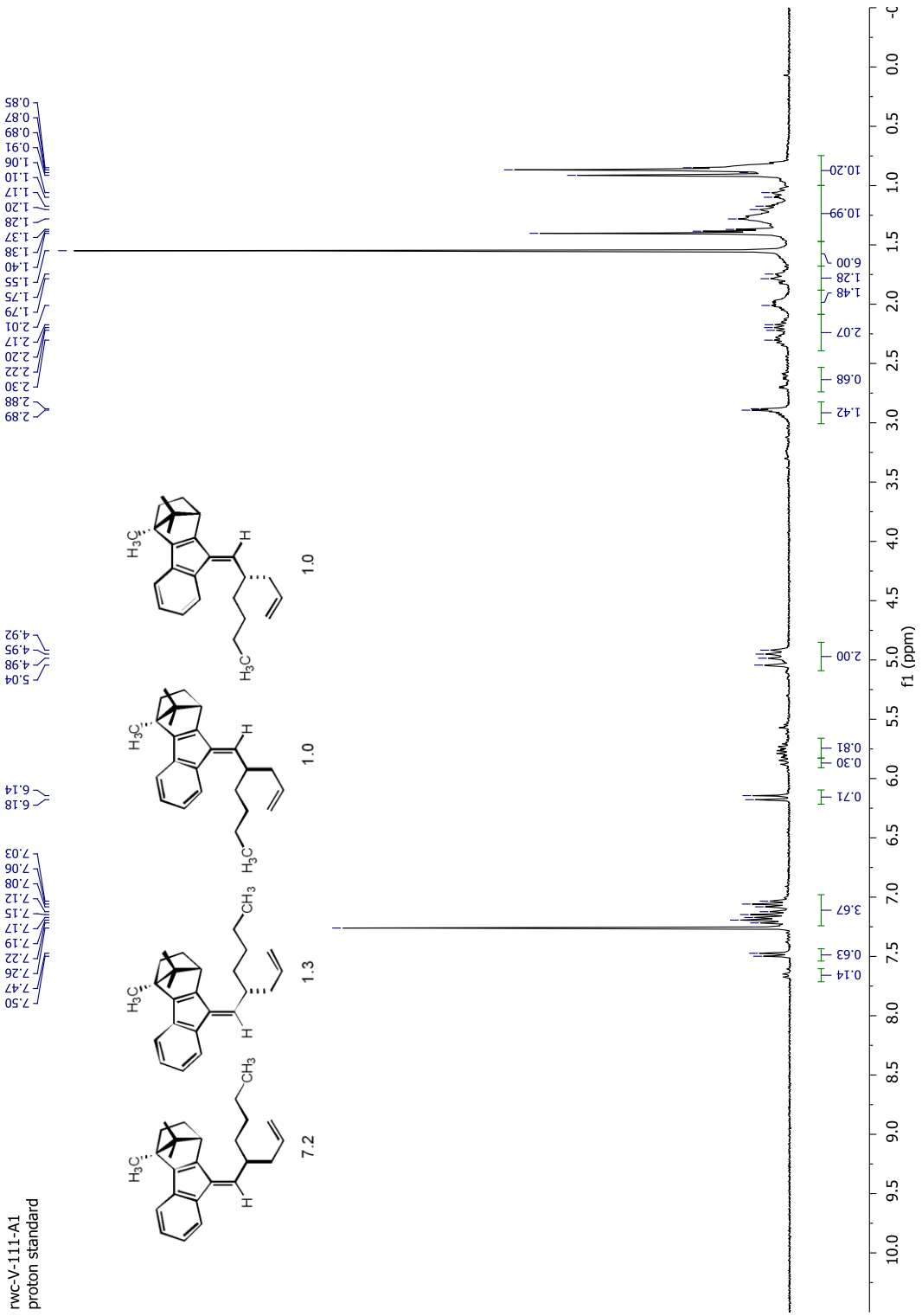
126.71
129.64
133.28
135.03
138.13
140.86
145.69
154.35
f1 (ppm)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proton standard
f1 (ppm)
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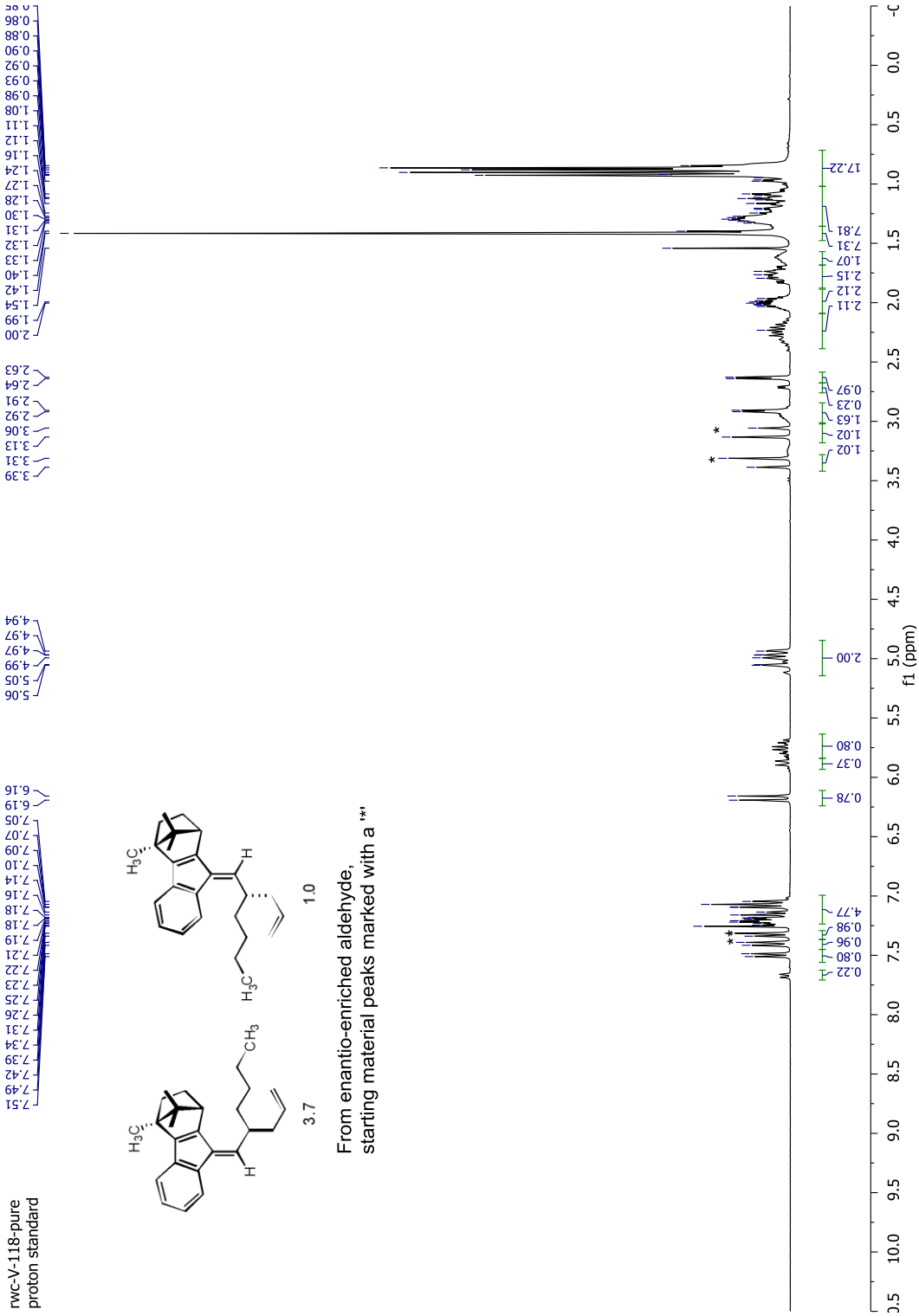
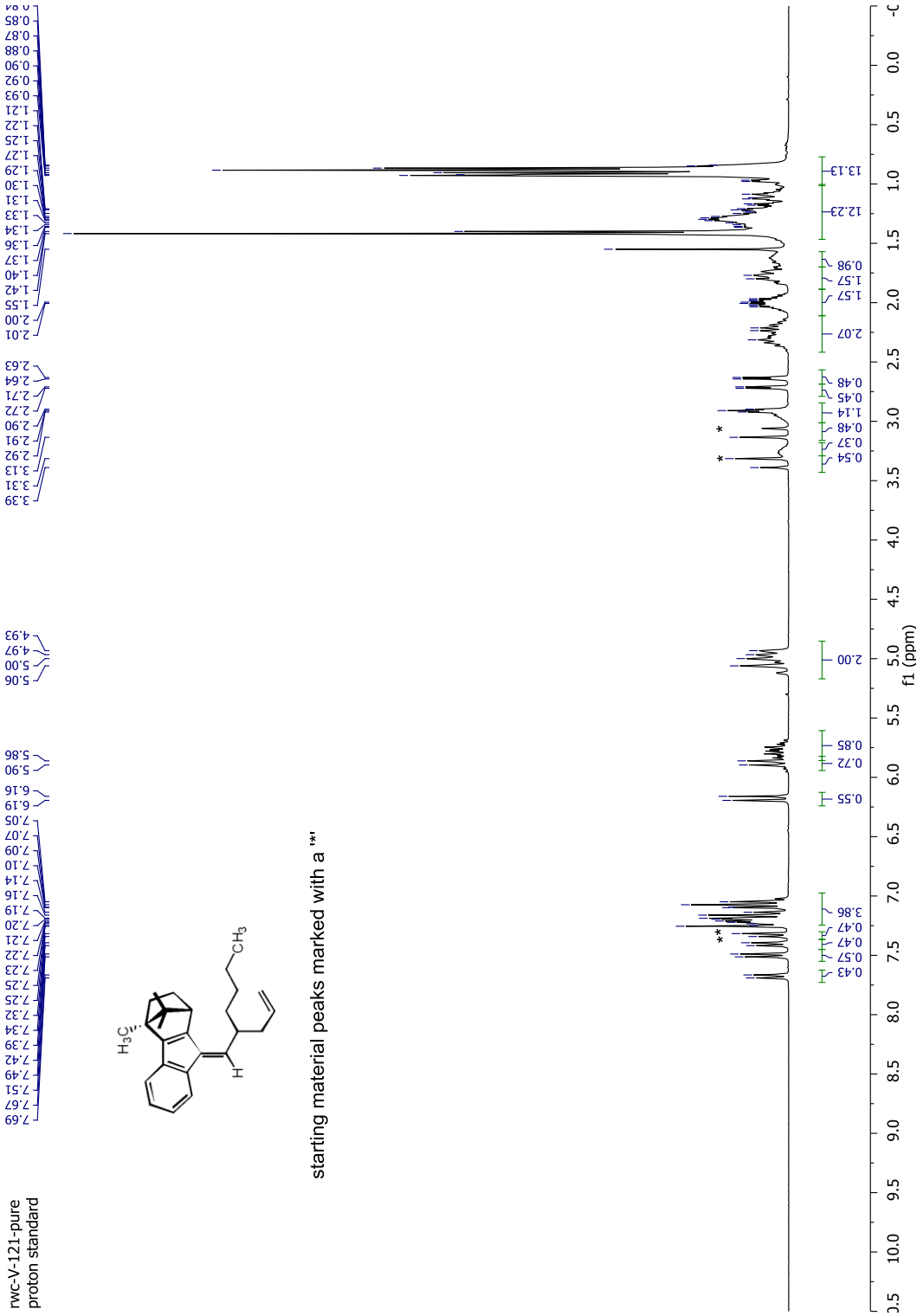
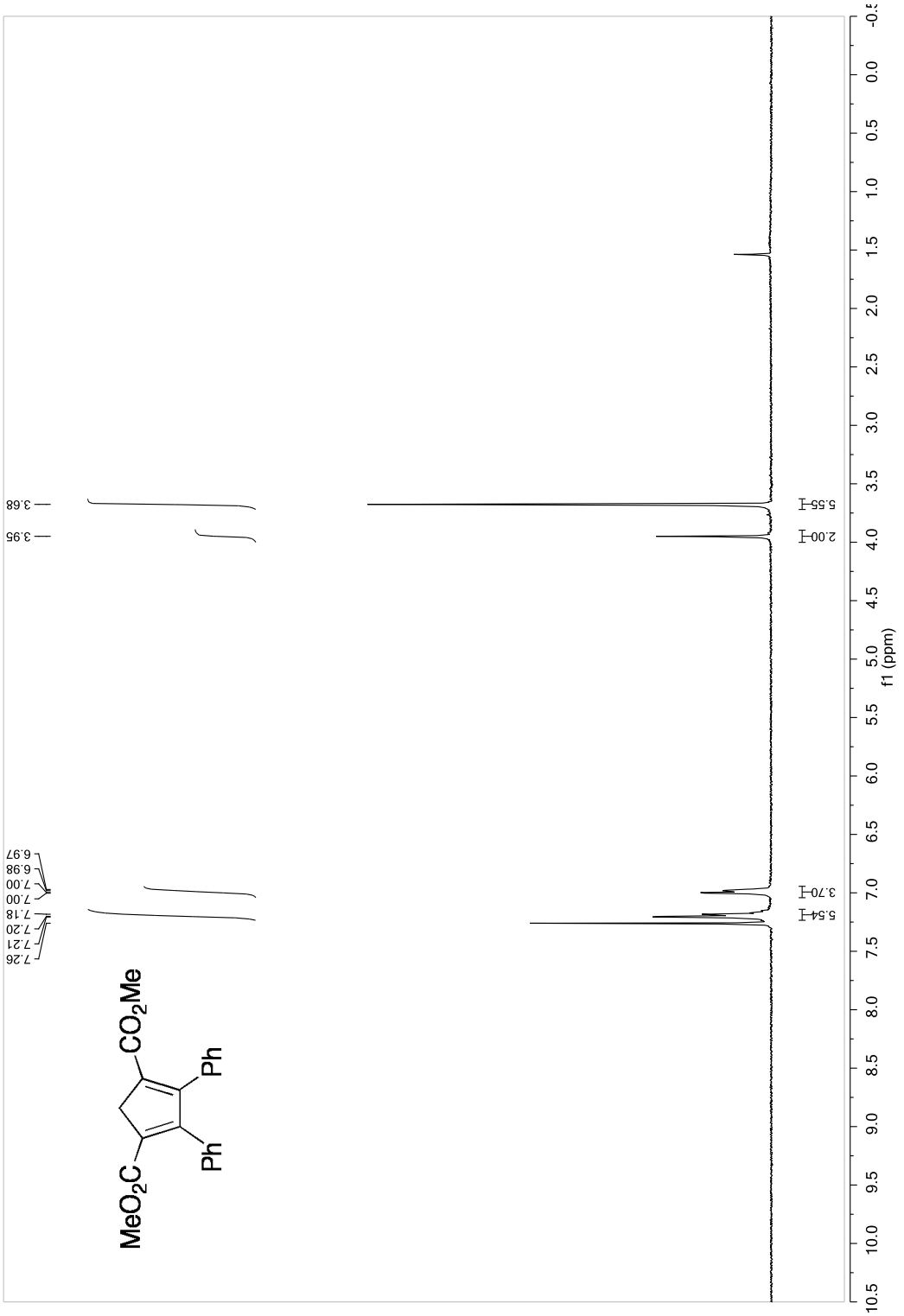
1.0
1.3
7.2


rwc-V-118-pure
proton standard
From enantio-enriched aldehyde,
starting material peaks marked with a '*'
1.0
3.7
f1 (ppm)


rwc-V-121-pure
proton standard
starting material peaks marked with a '*'
f1 (ppm)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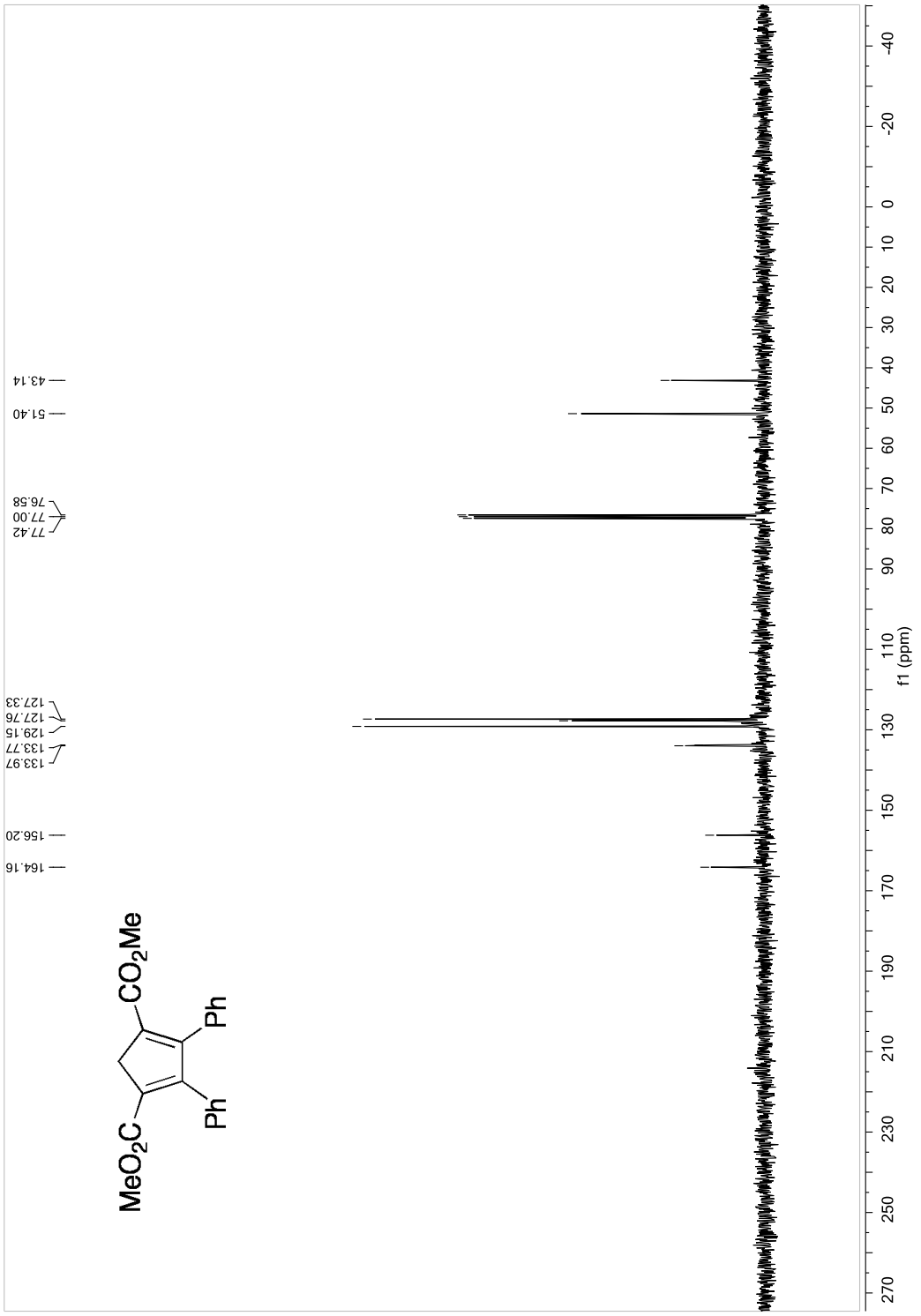
5.55
2.00
f1 (ppm)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CO2Me
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Ph
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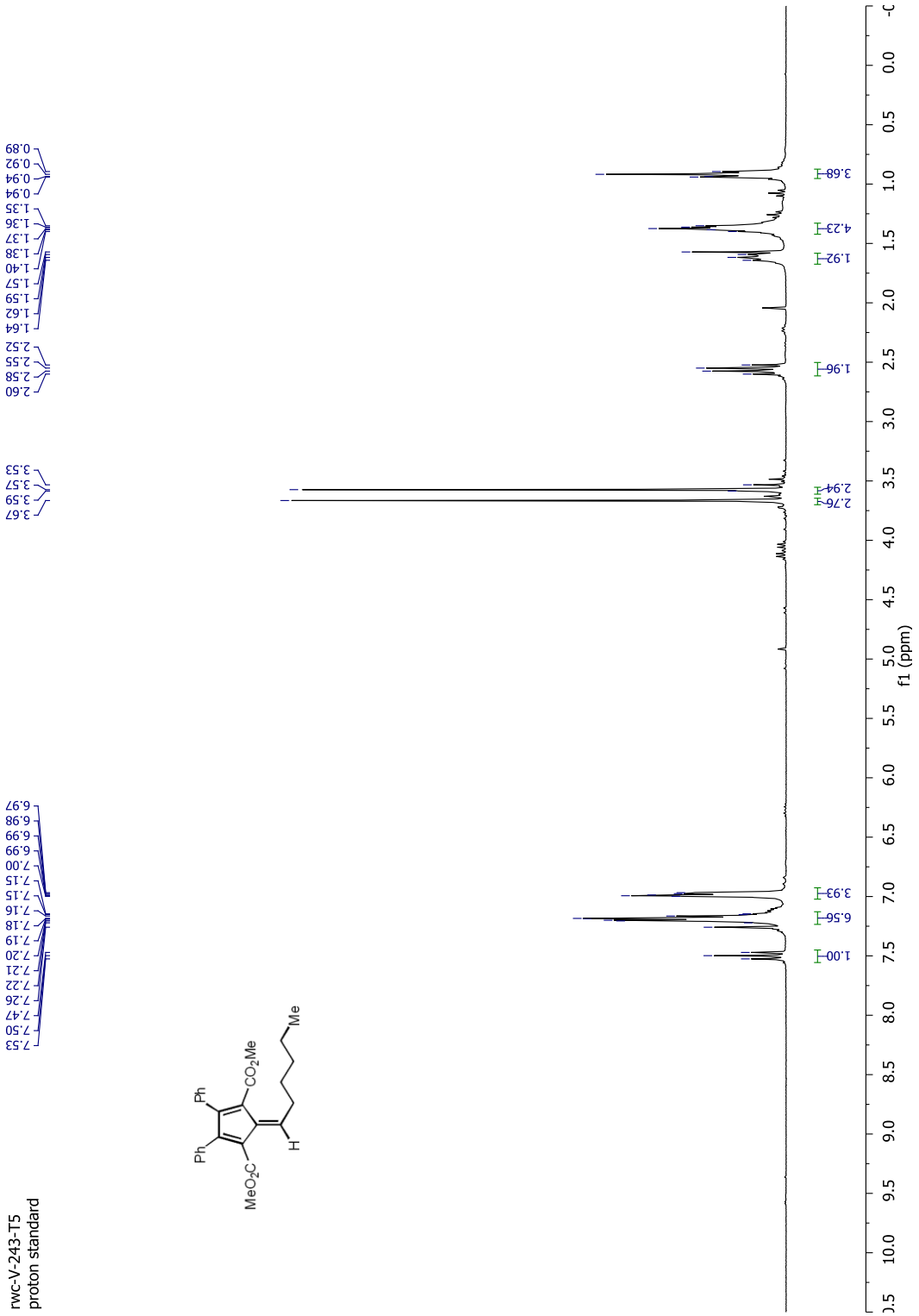
51.40
43.14
f1 (ppm)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Ph
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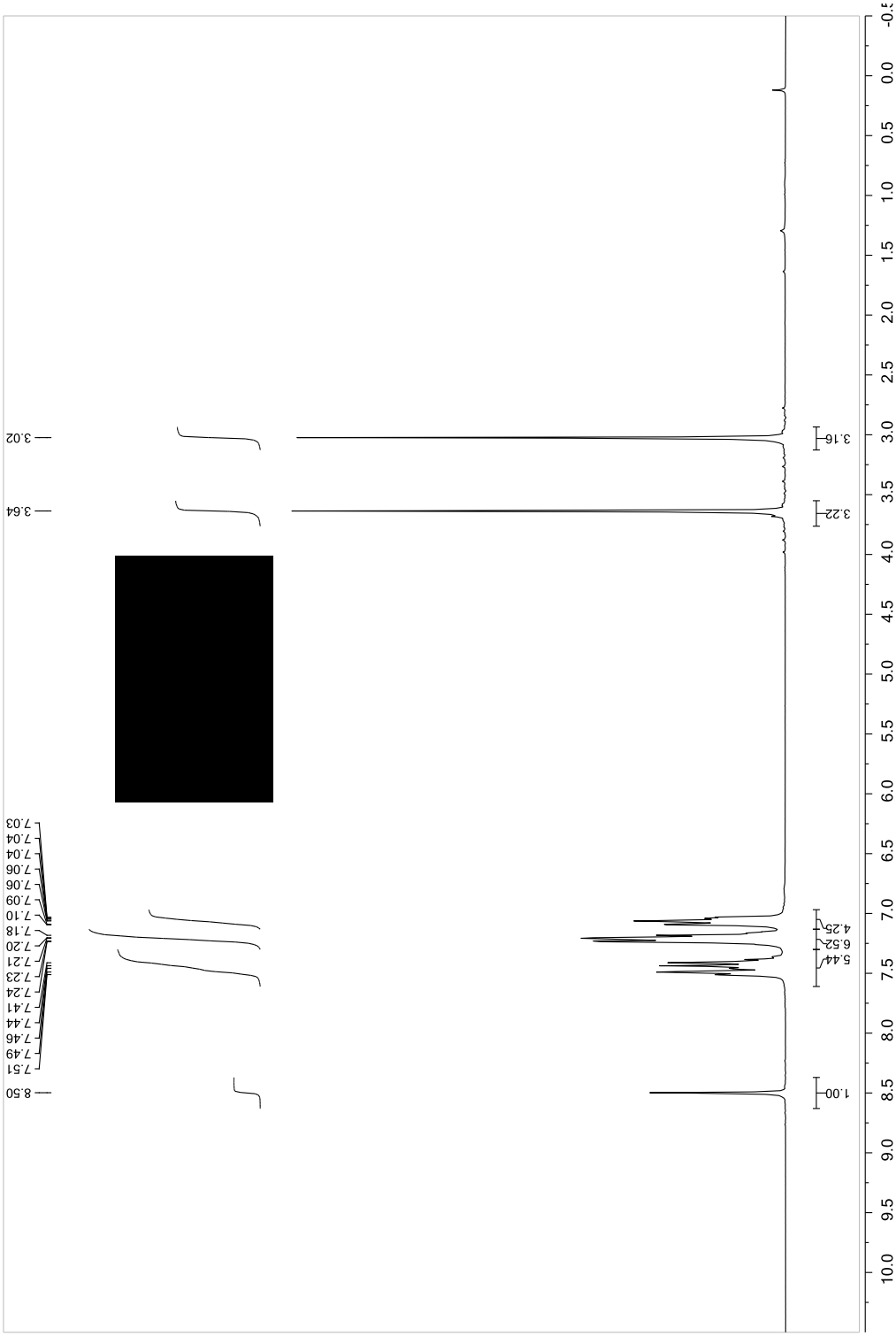
MeO2C
Me
H
f1 (ppm)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7.09
7.06
7.06
7.04
7.04
7.03
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3.02
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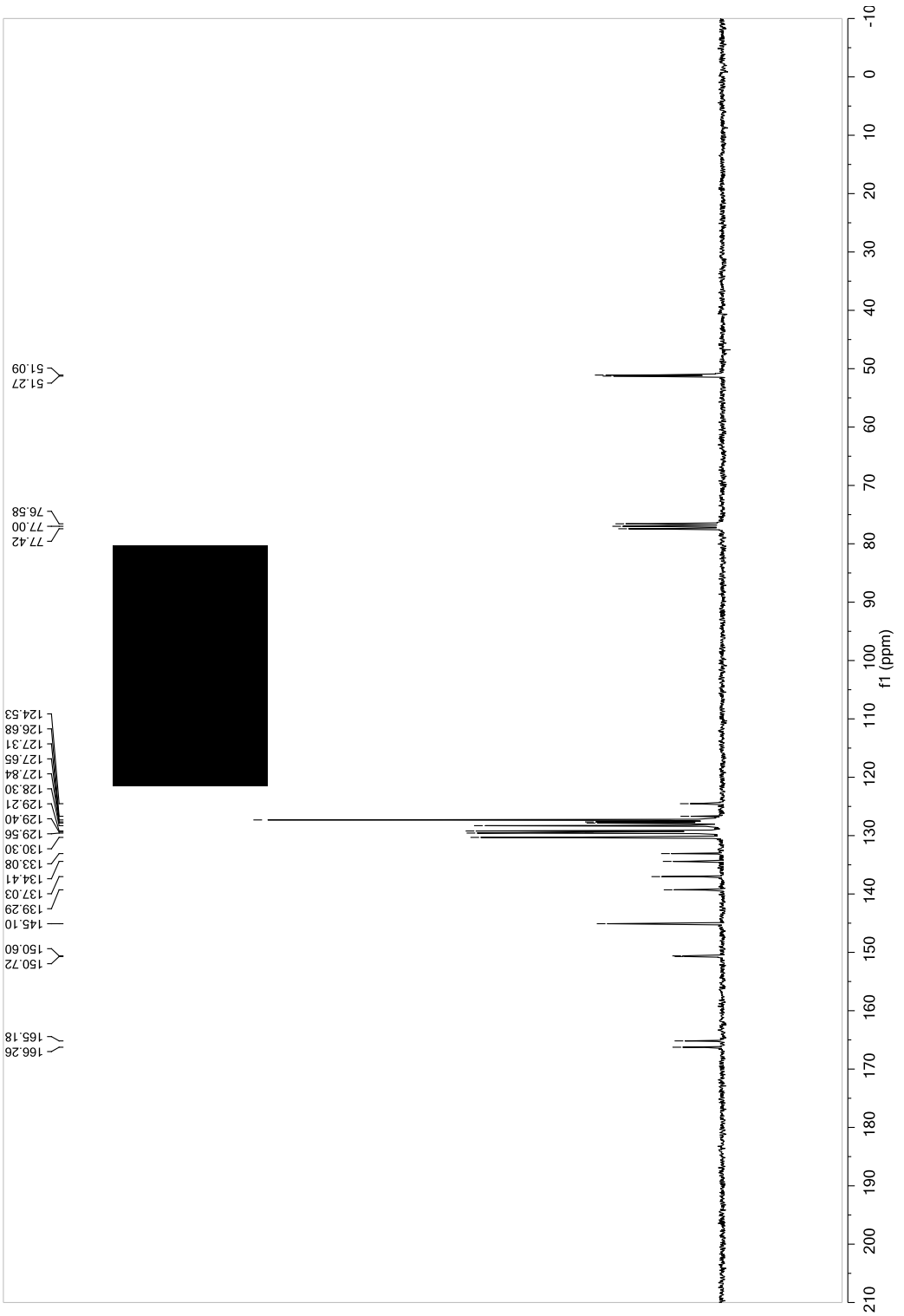
3.22
3.16
f1 (ppm)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134.41
133.08
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129.21
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124.53
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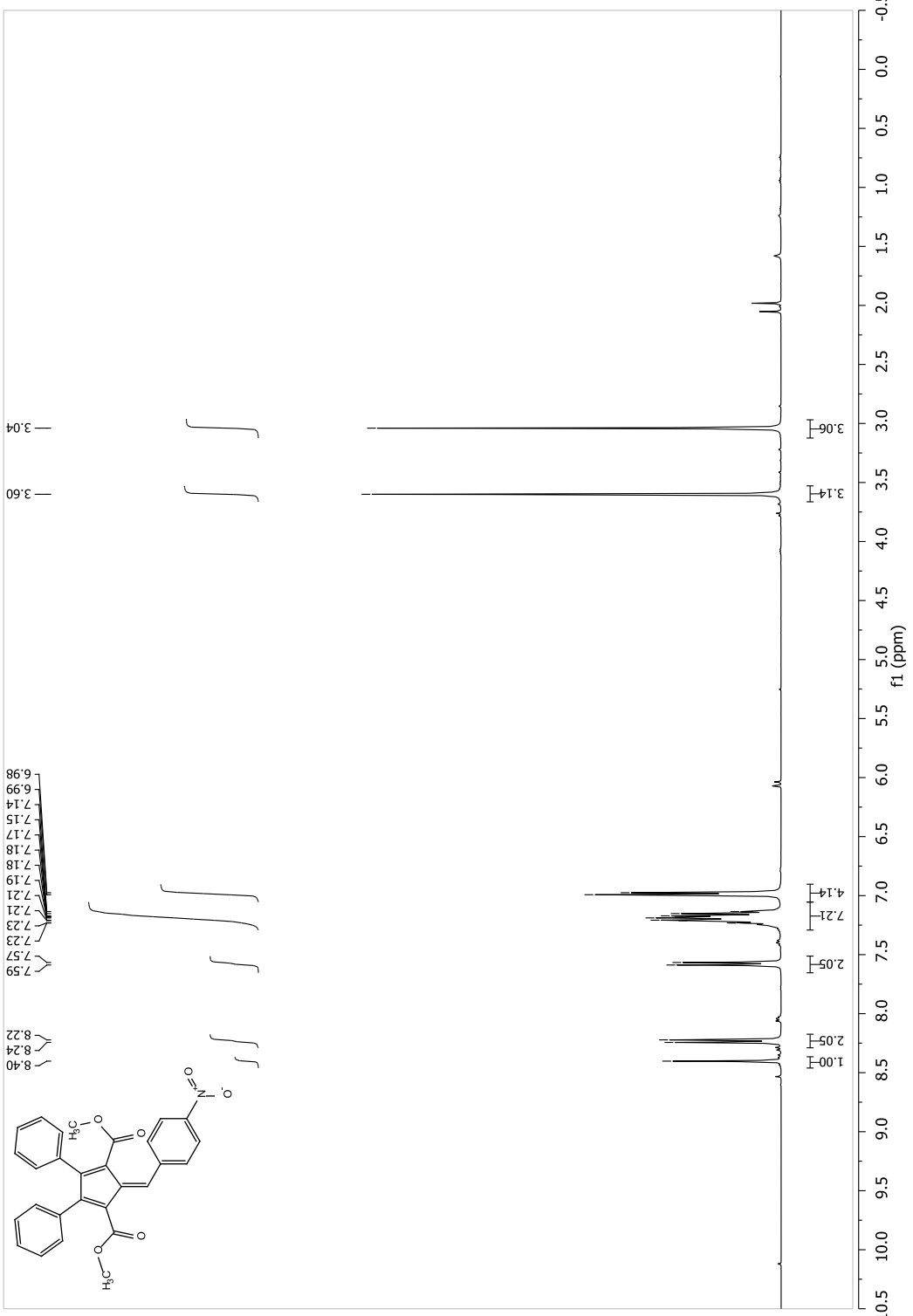
77.00
76.58
51.27
51.09
f1 (ppm)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7.17
7.15
7.14
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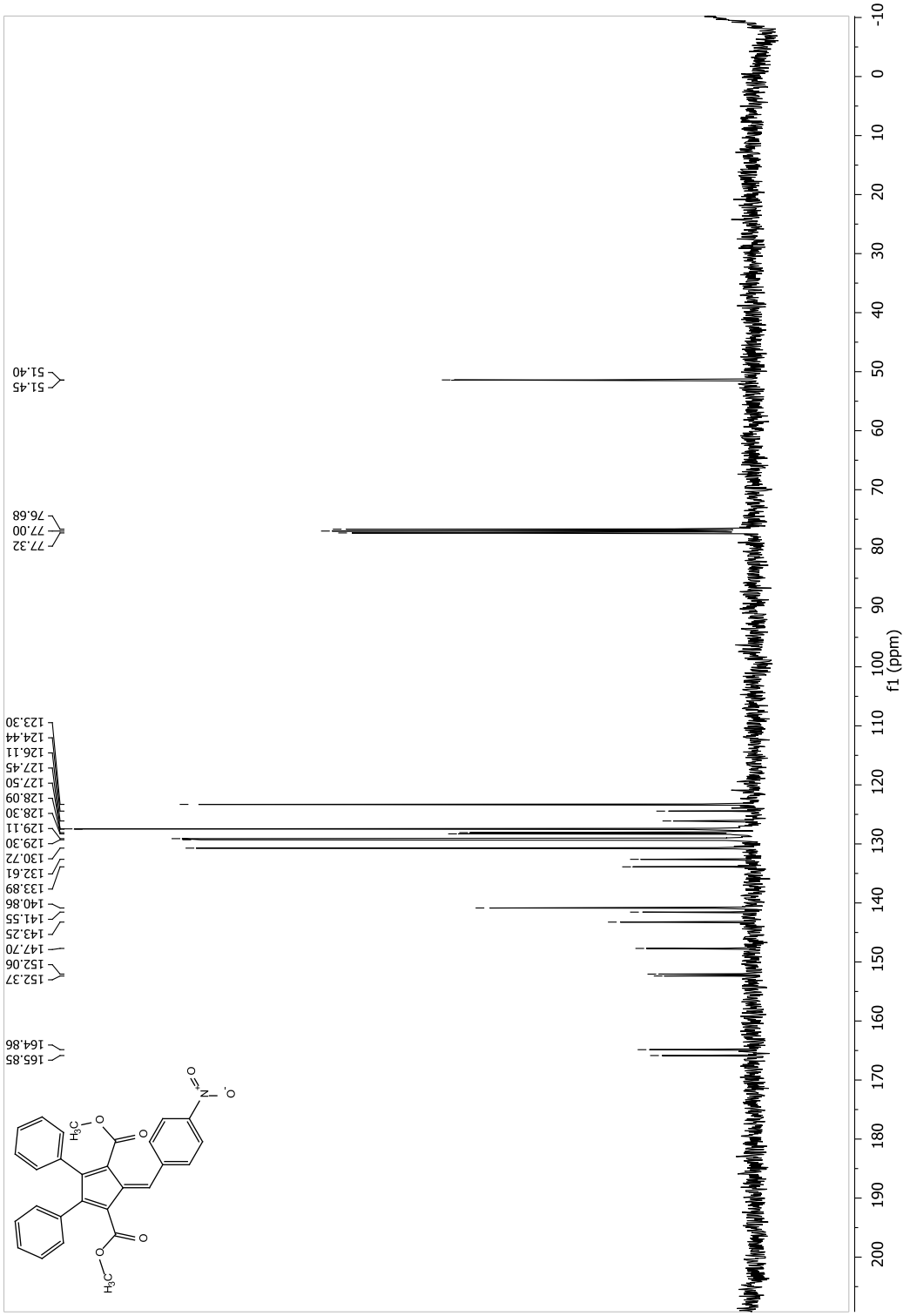
2.05
7.21
4.14
3.14
3.06
f1 (ppm)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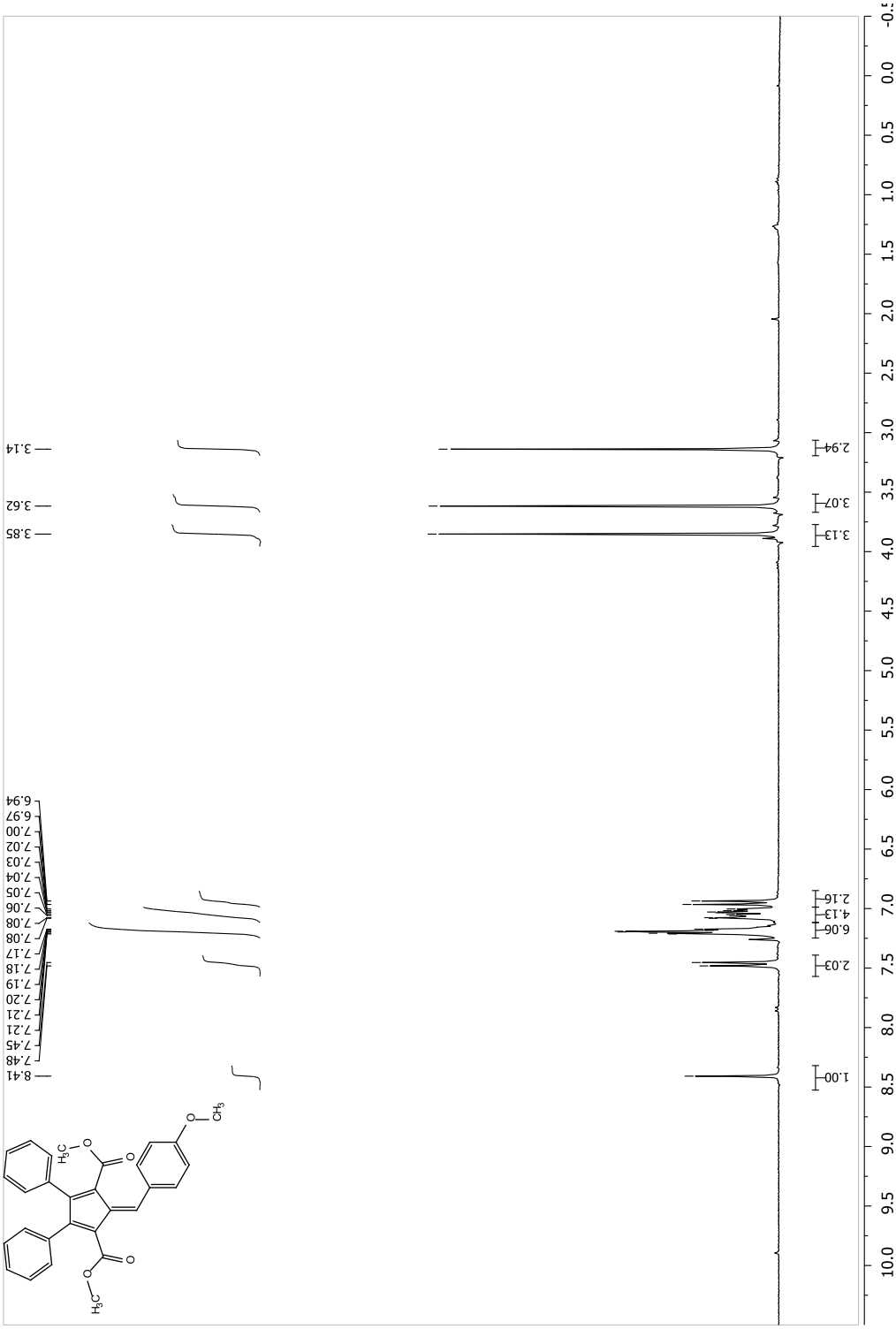
77.00
76.68
51.45
51.40
f1 (ppm)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7.05
7.04
7.03
7.02
7.00
6.97
6.94
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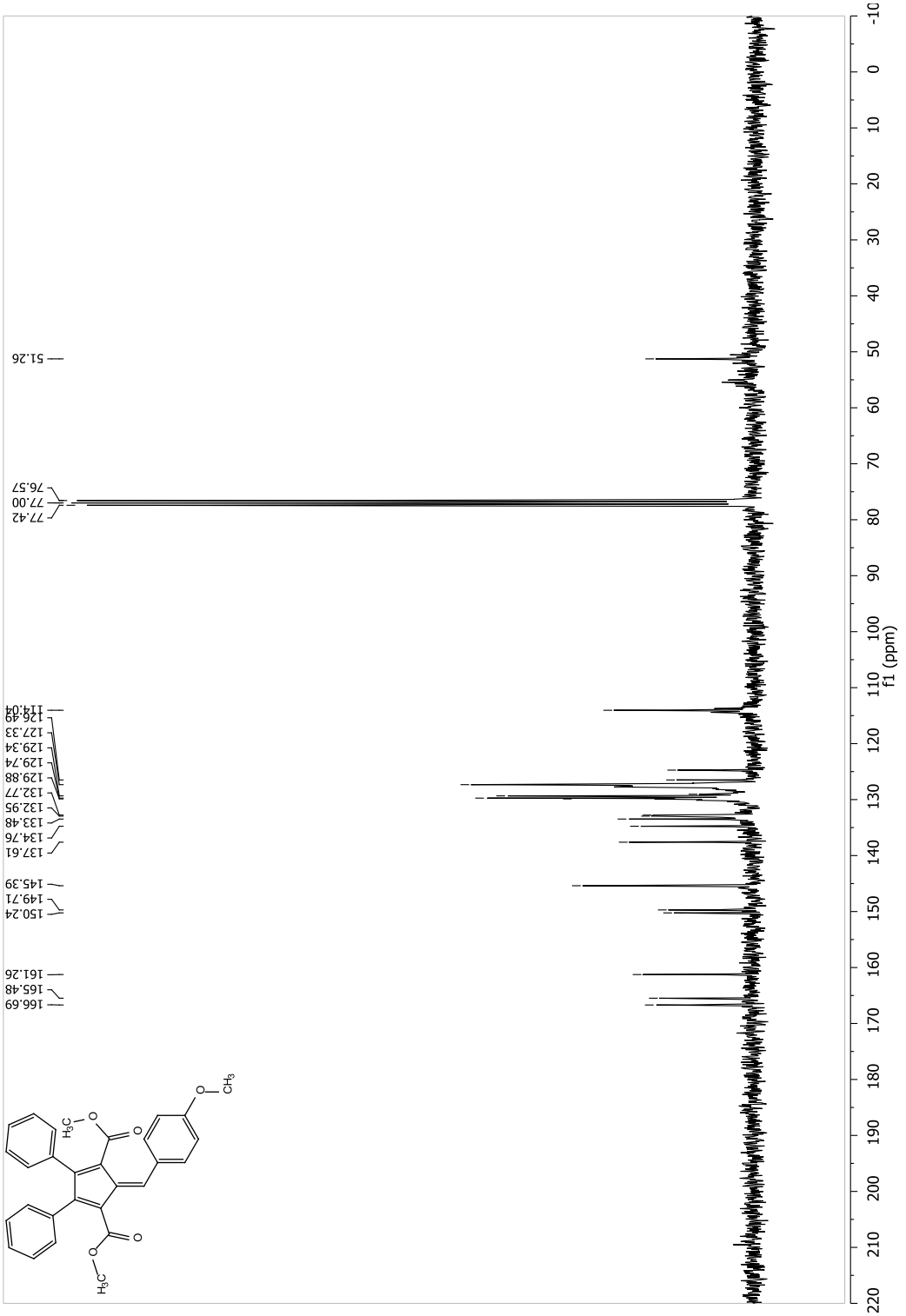
3.13
3.07
2.94
f1 (ppm)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77.00
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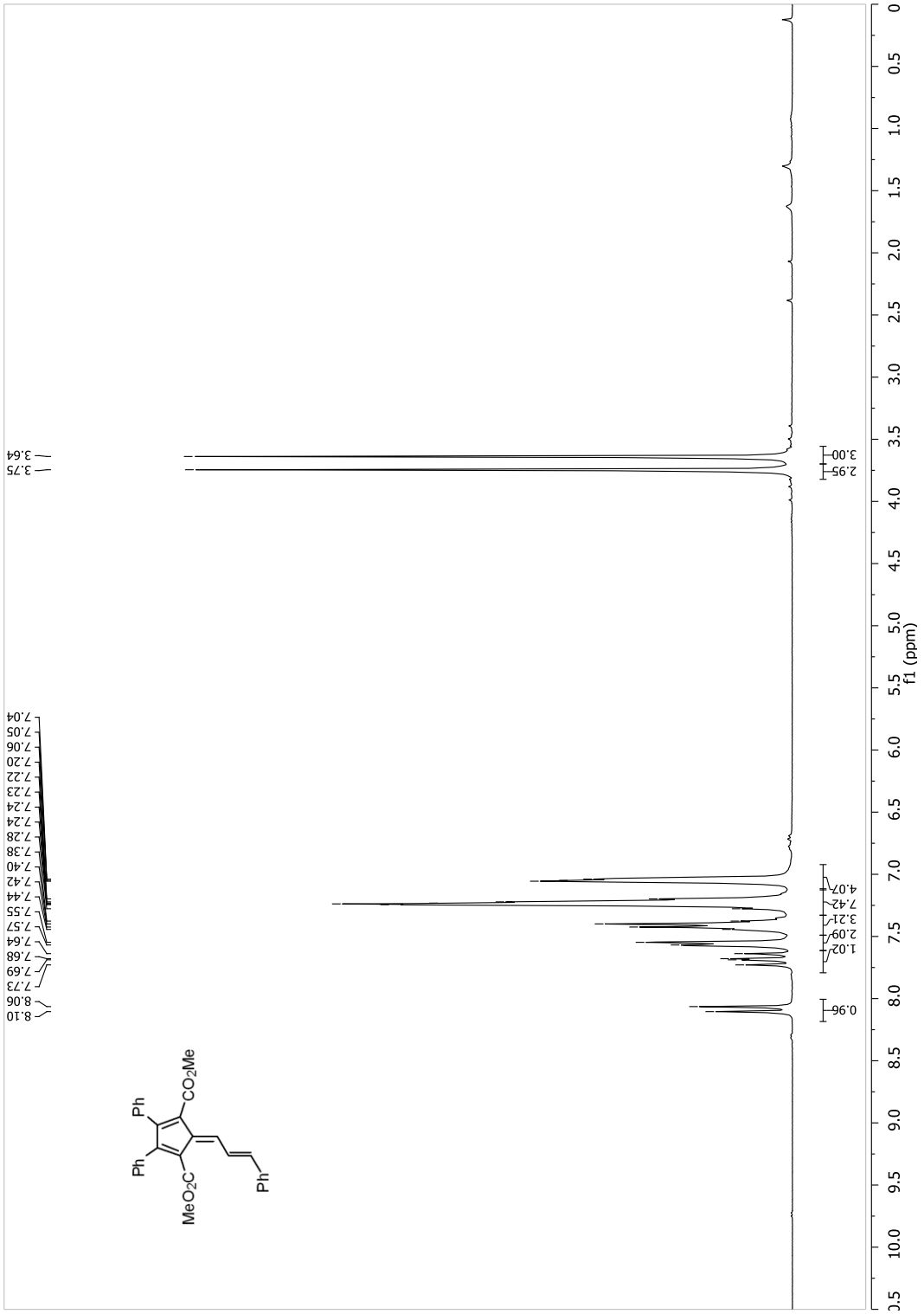
f1 (ppm)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7.28
7.24
7.24
7.23
7.22
7.20
7.06
7.05
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1.02
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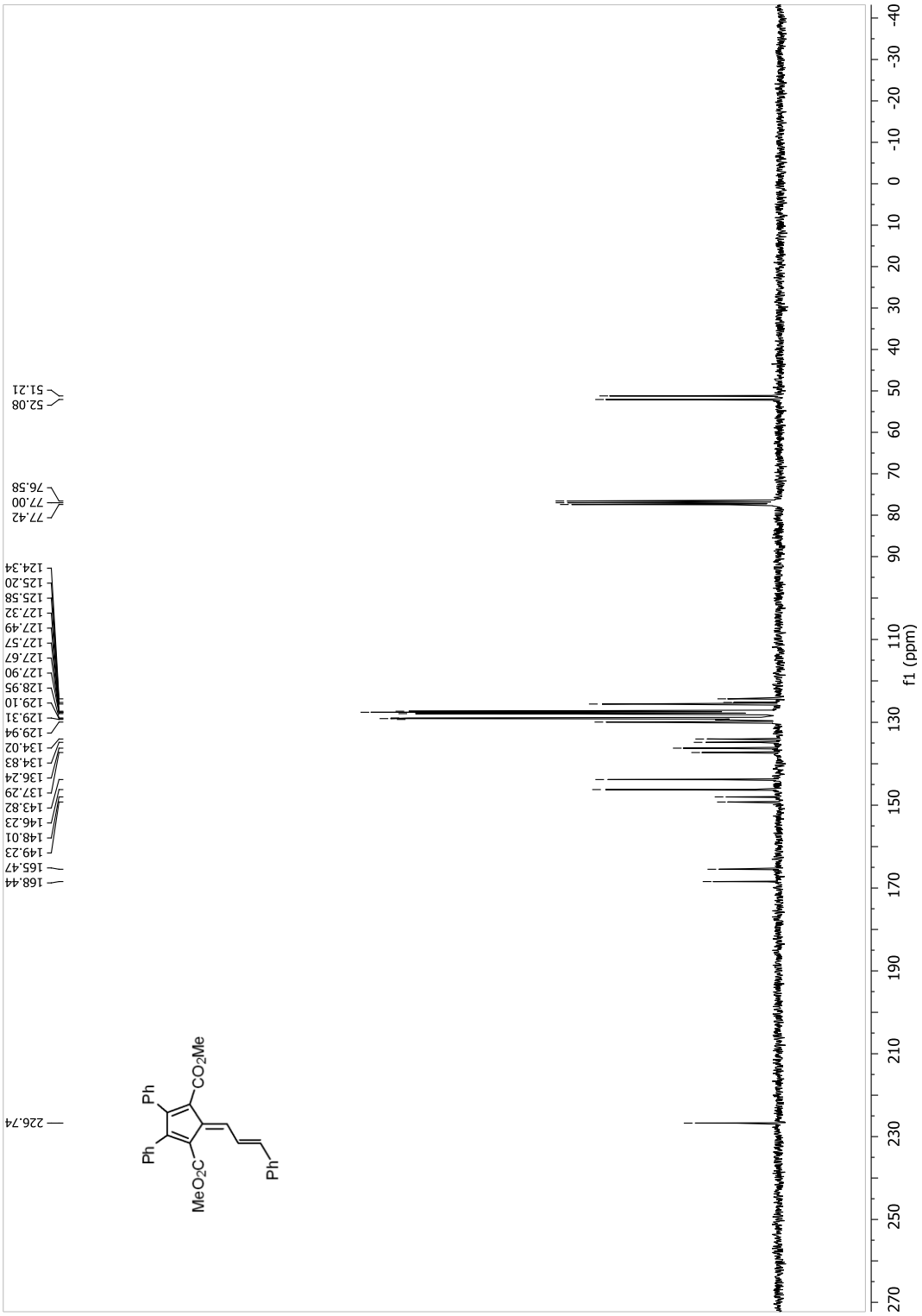
f1 (ppm)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127.32
125.58
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Ph
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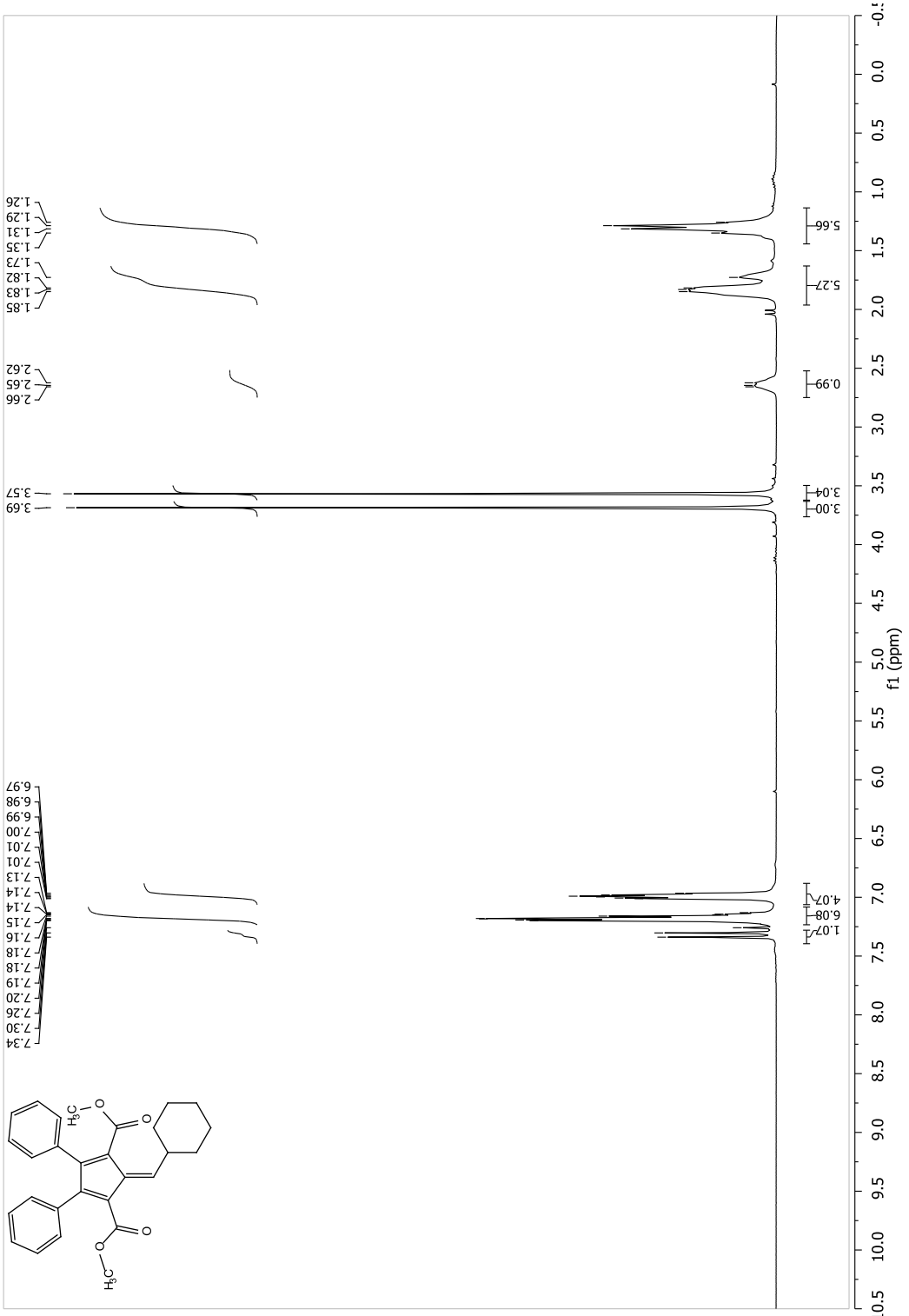
Ph
f1 (ppm)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4.0
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3.0
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2.0
1.5
1.0
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-0.5
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6.08
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3.00
3.04
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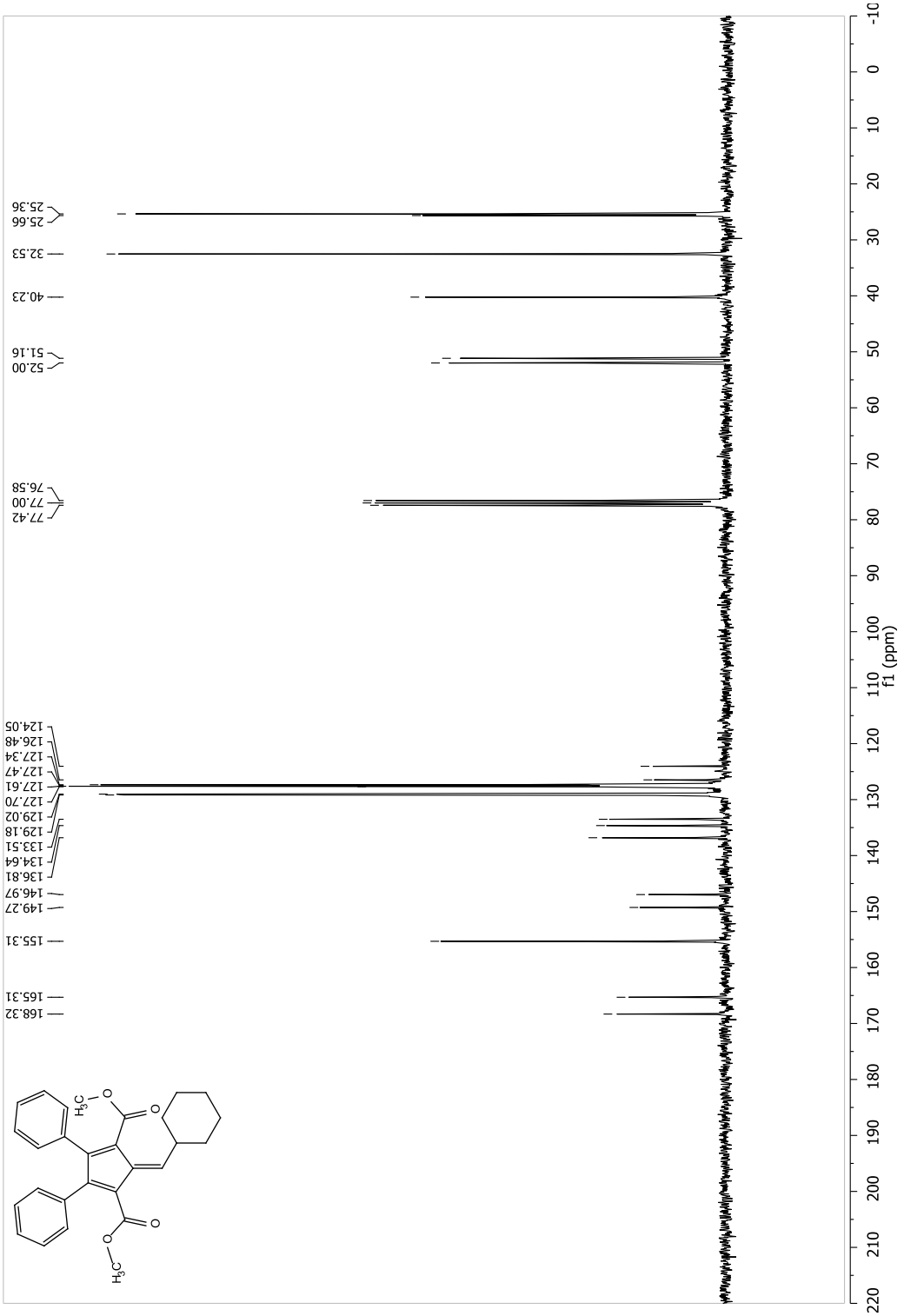
O
O
O
H3C
H3C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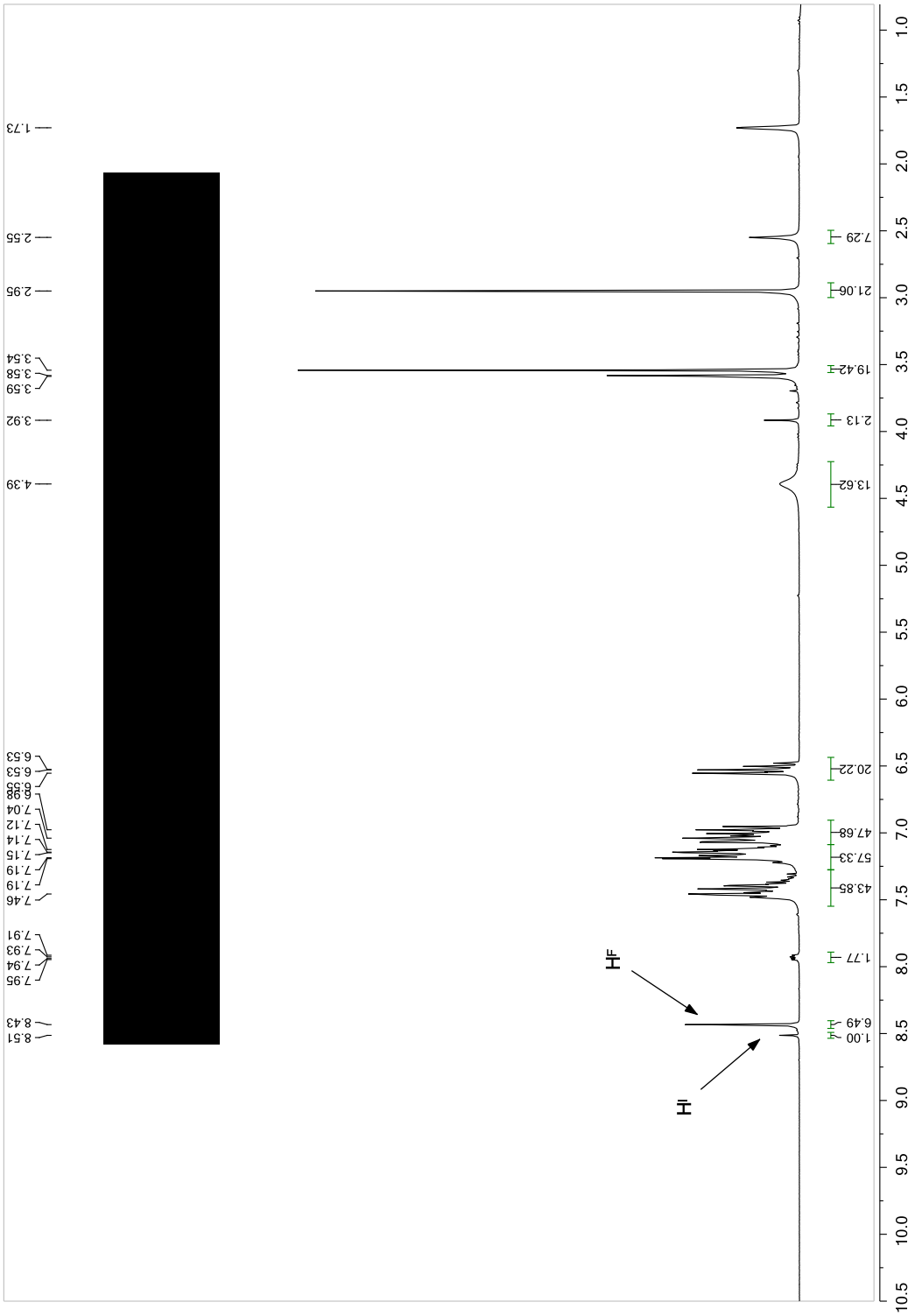
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1.00
6.49
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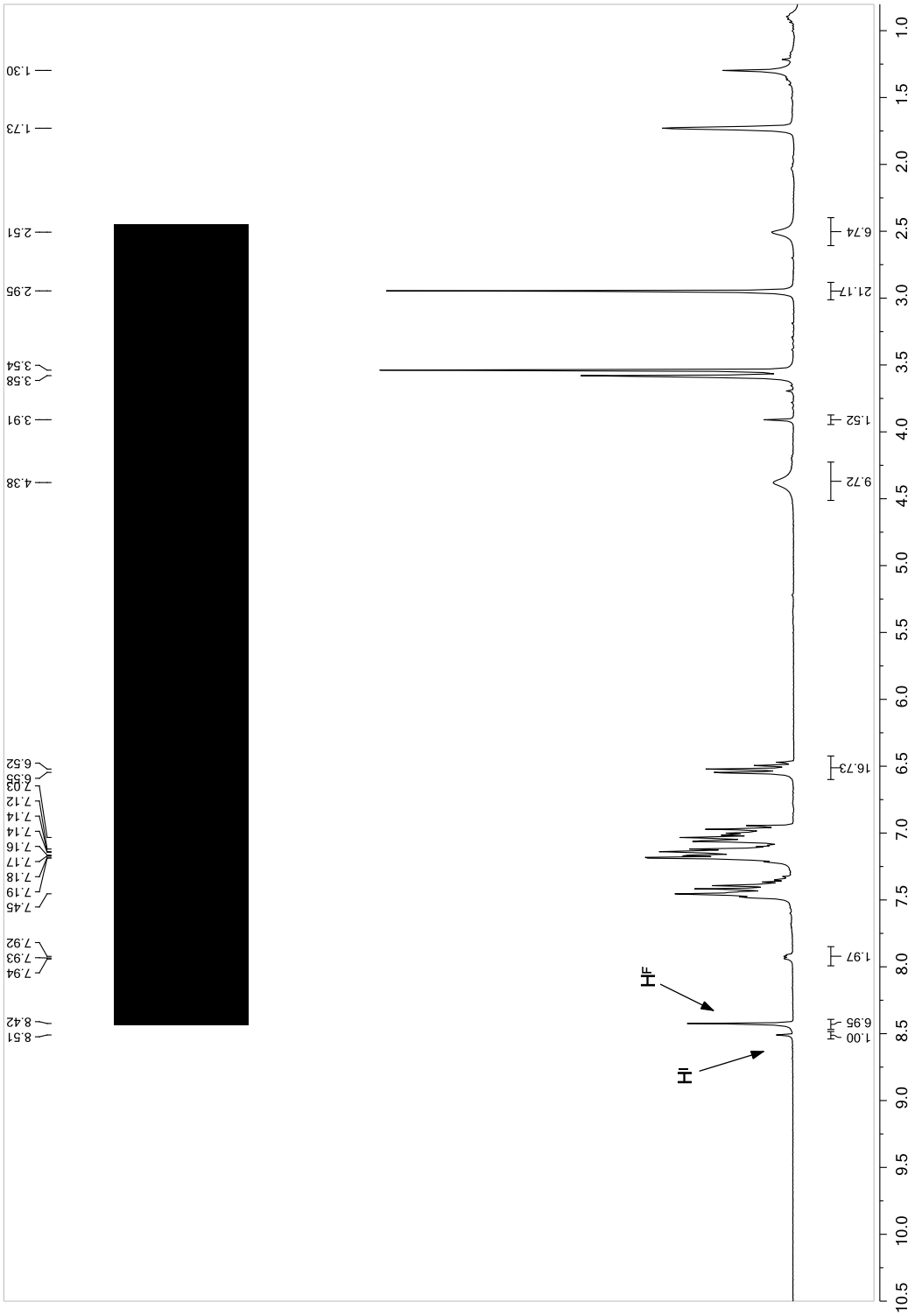
19.42
21.06
7.29
Hᵢ
Hₑ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7.14
7.16
7.17
7.18
7.19
7.45
7.92
7.93
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HI
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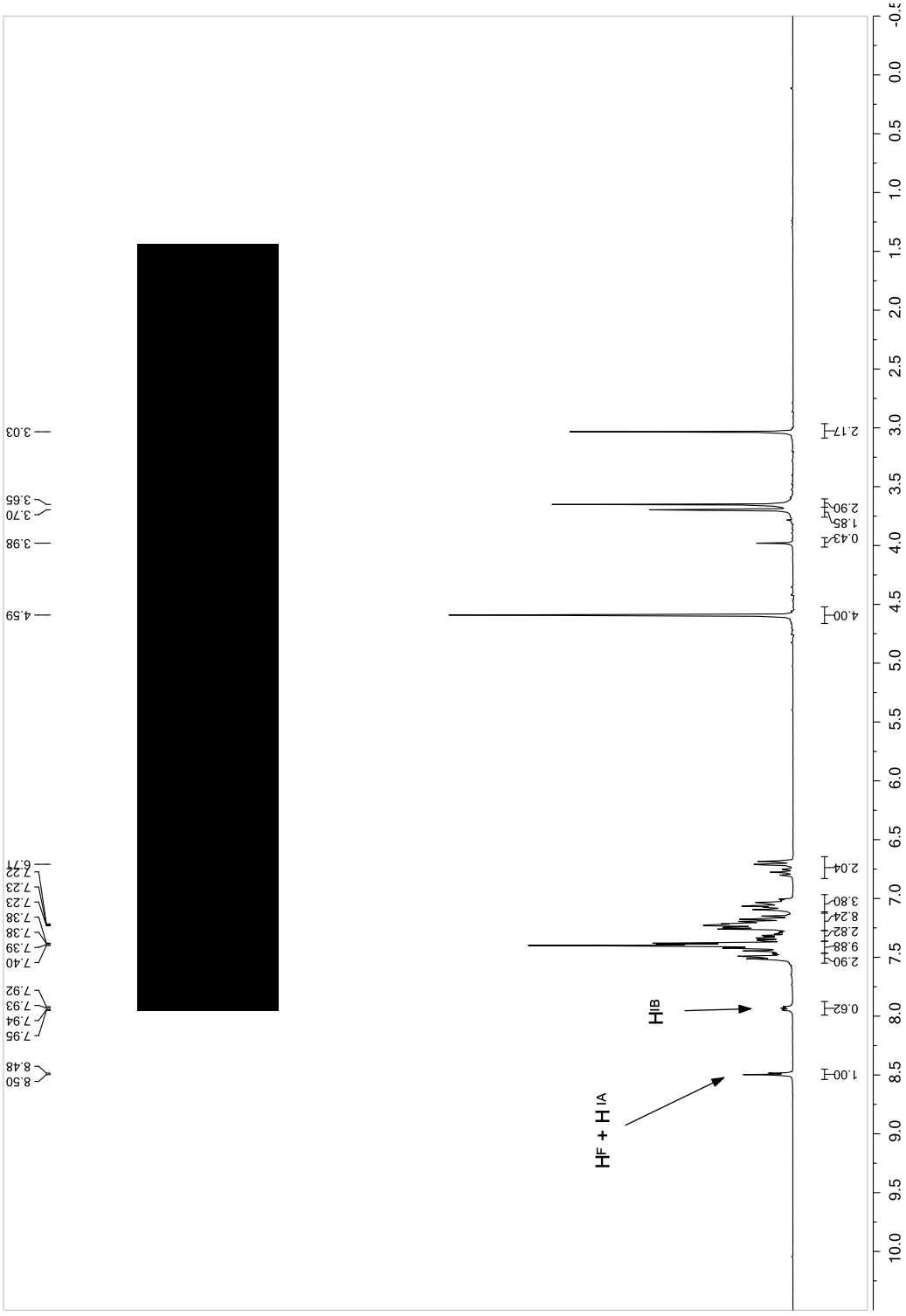
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6.71
4.59
3.98
3.70
3.65
3.03
1.00
0.62
2.90
9.88
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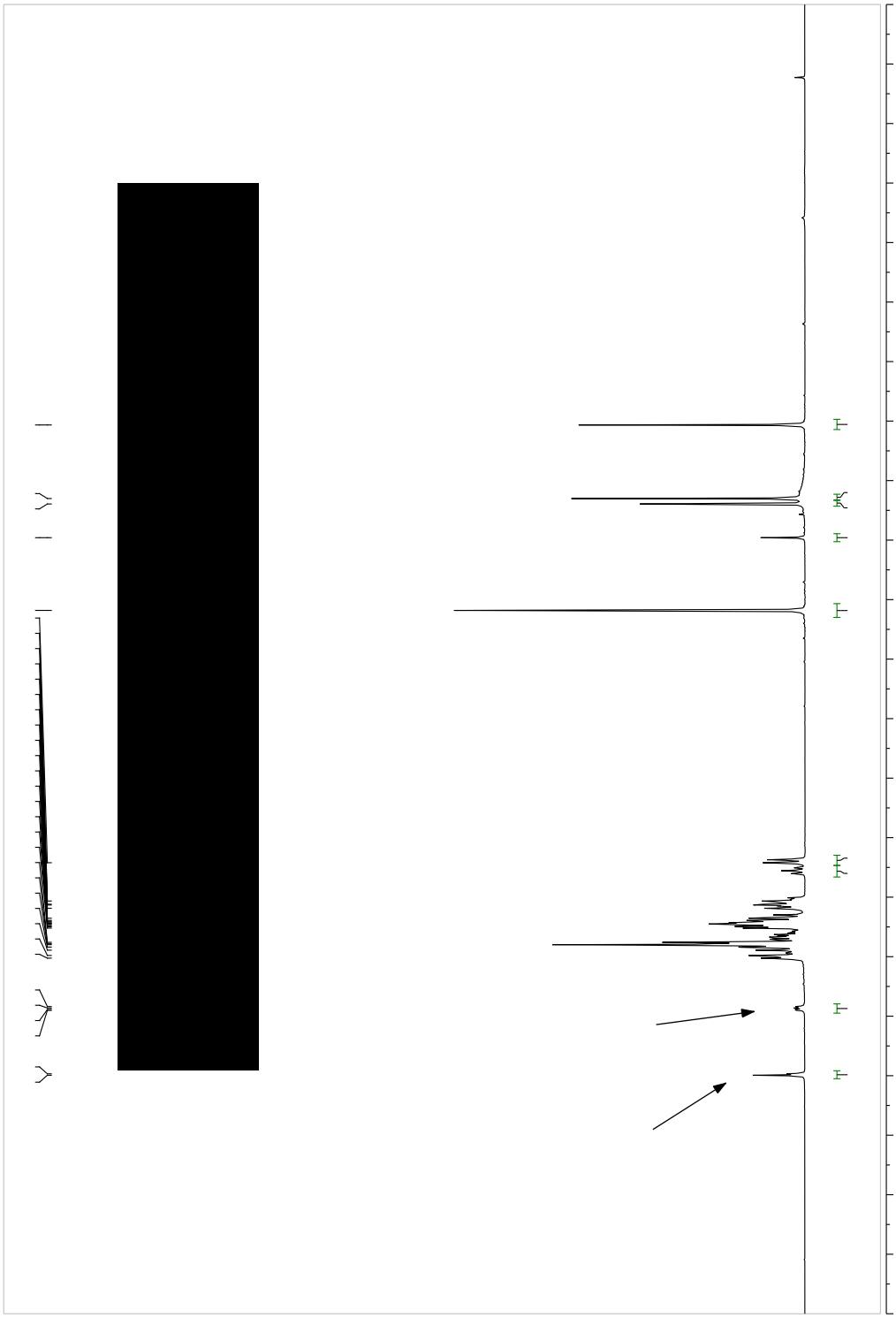
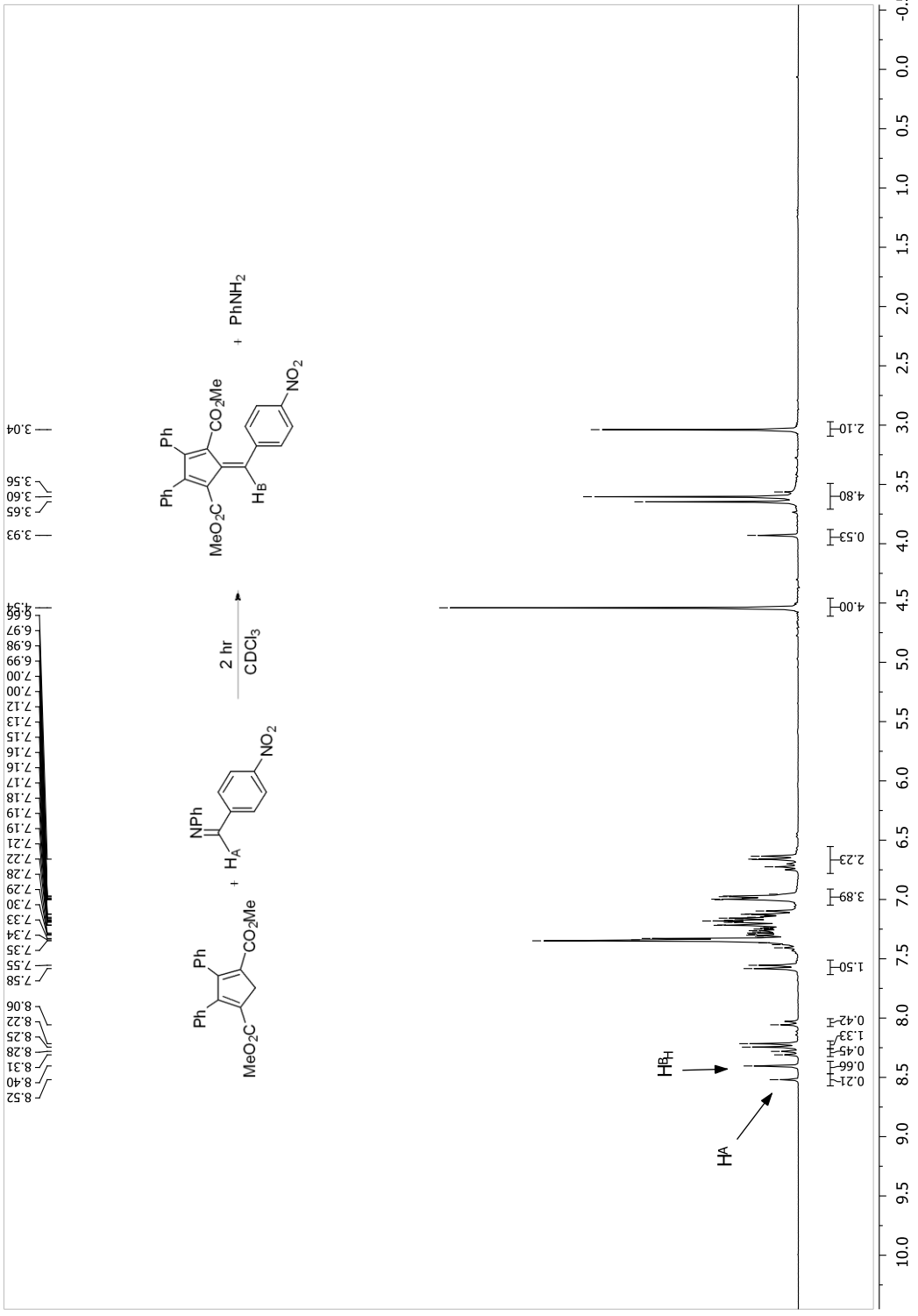
3.80
2.04
4.00
0.43
1.85
2.90
2.17
HF + HVI
HIB

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Ph
CO2Me
MeO2C
NPh
HA
NO2
+
2 hr
CDCl3
HB
PhNH2
HA
HB
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8.40
8.31
8.28
8.25
8.22
8.06
7.58
7.55
7.35
7.34
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7.28
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3.65
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3.56
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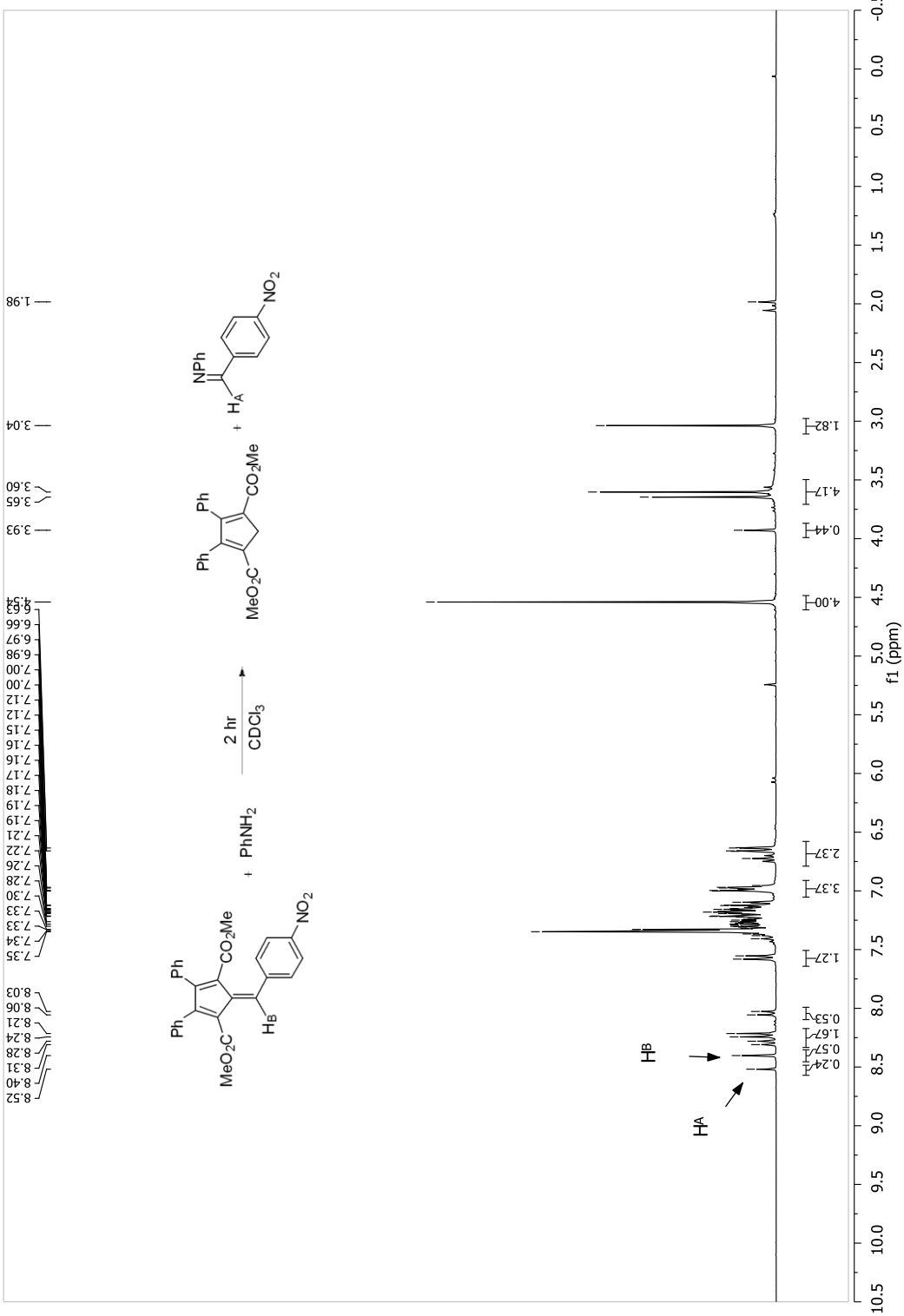
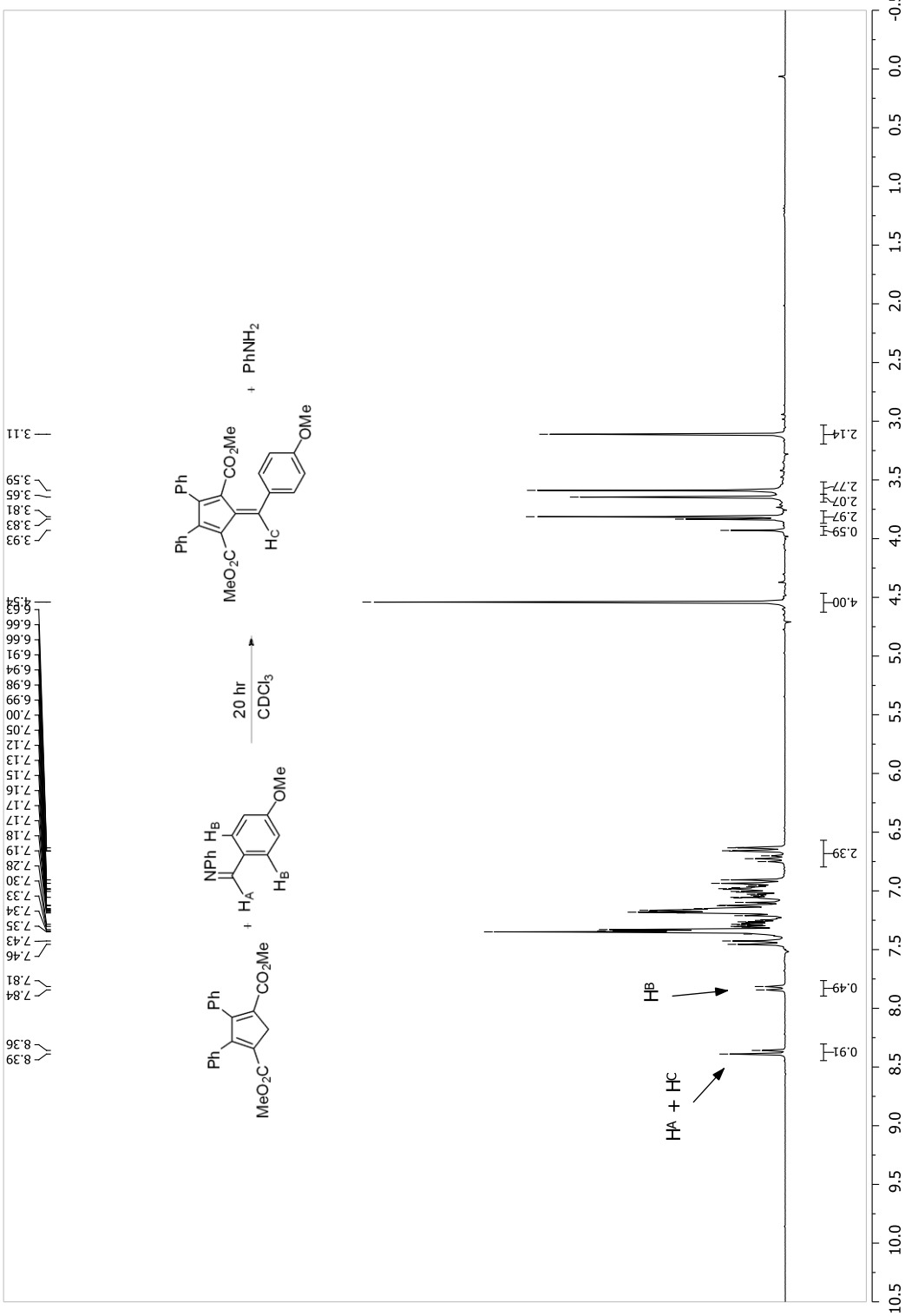
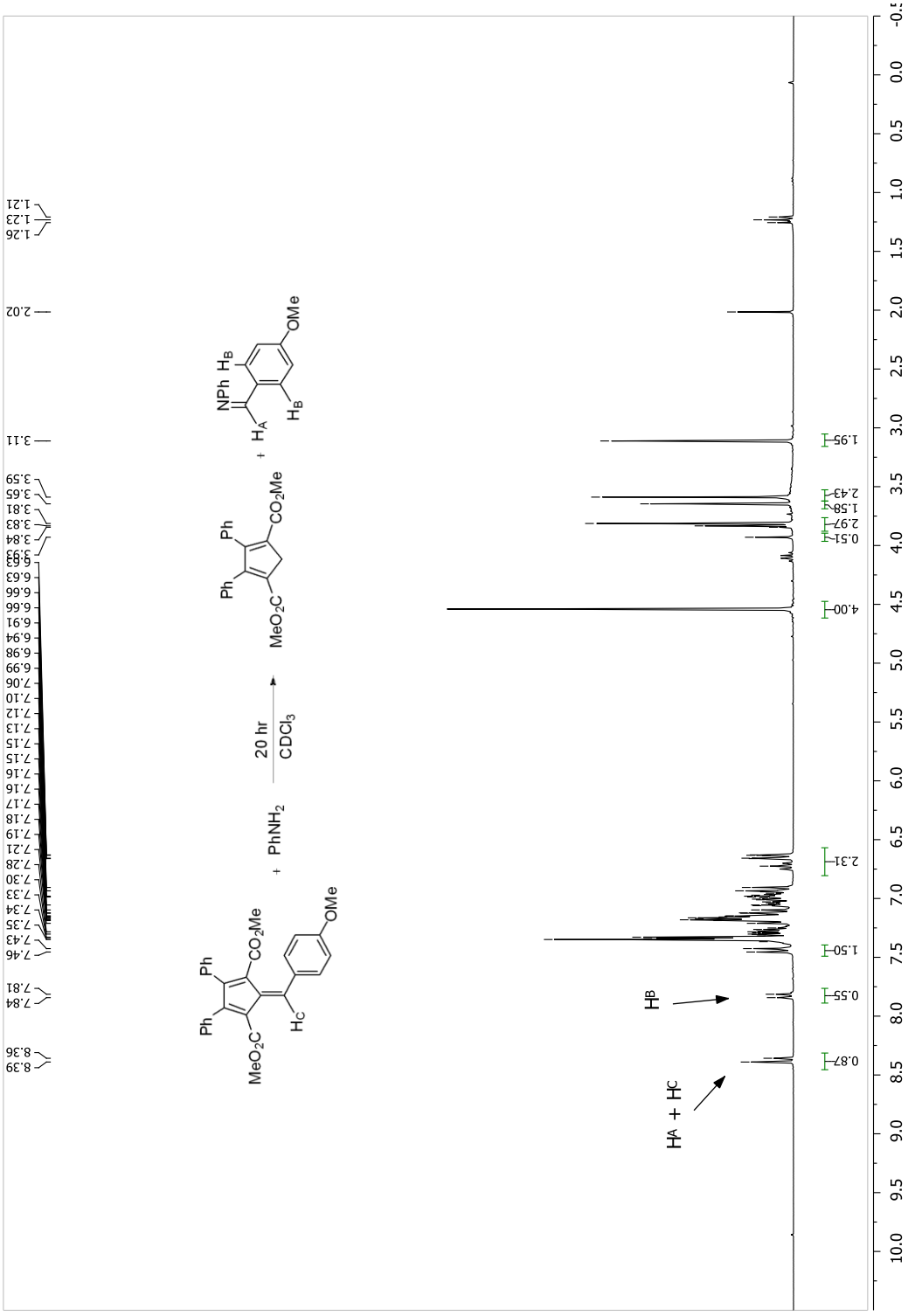
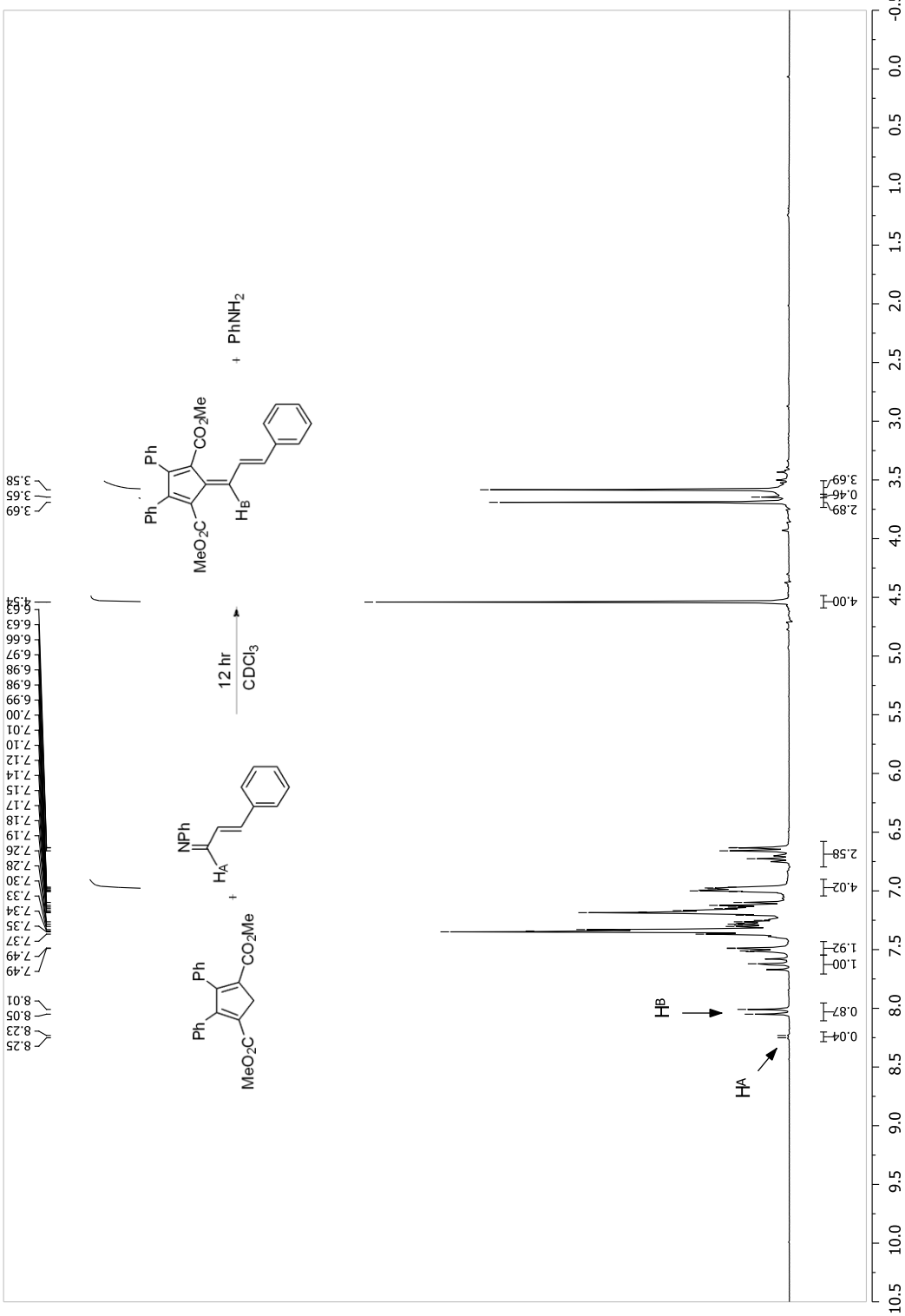
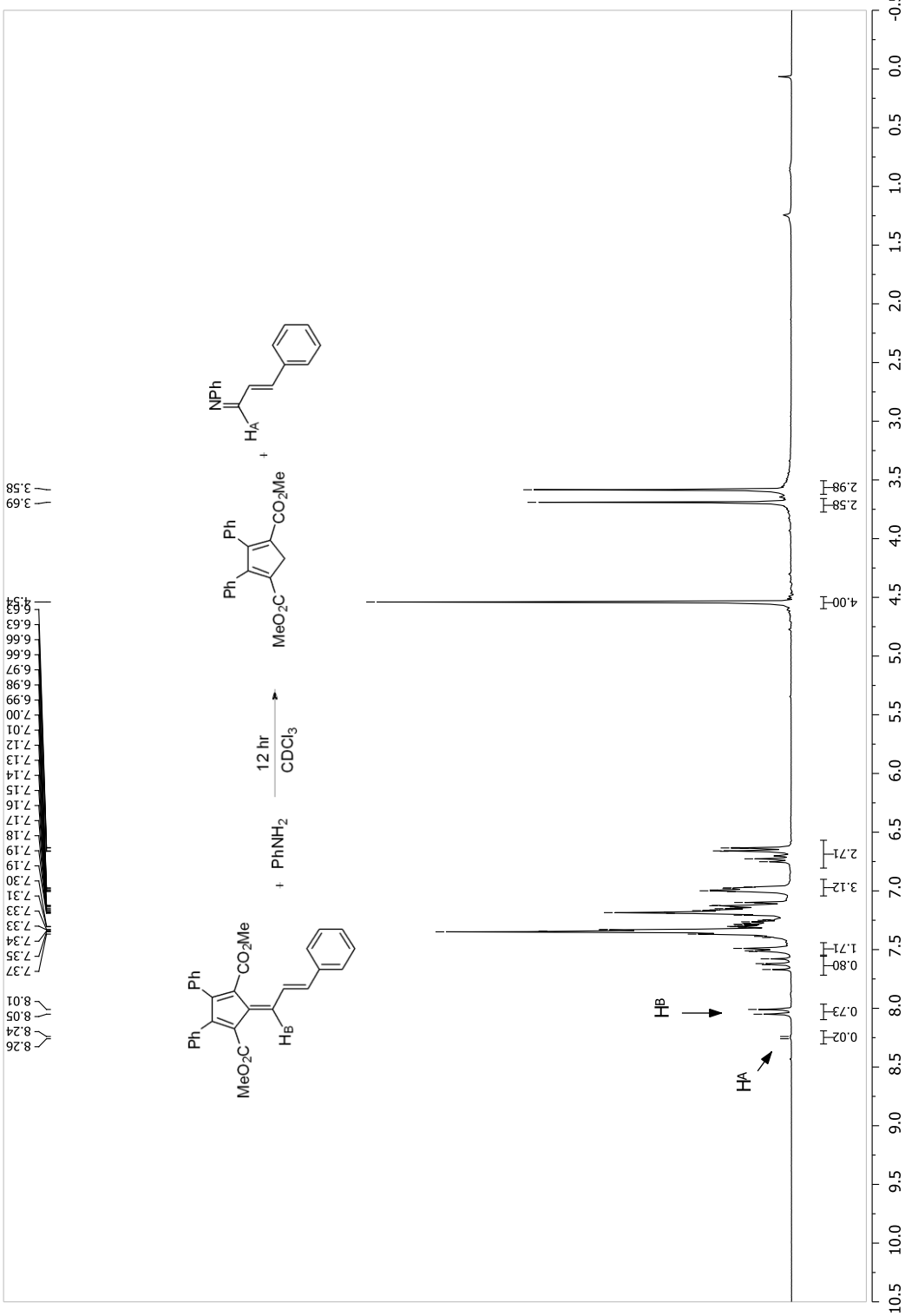
0.42
1.50
3.89
2.23
4.00
0.53
4.80
2.10

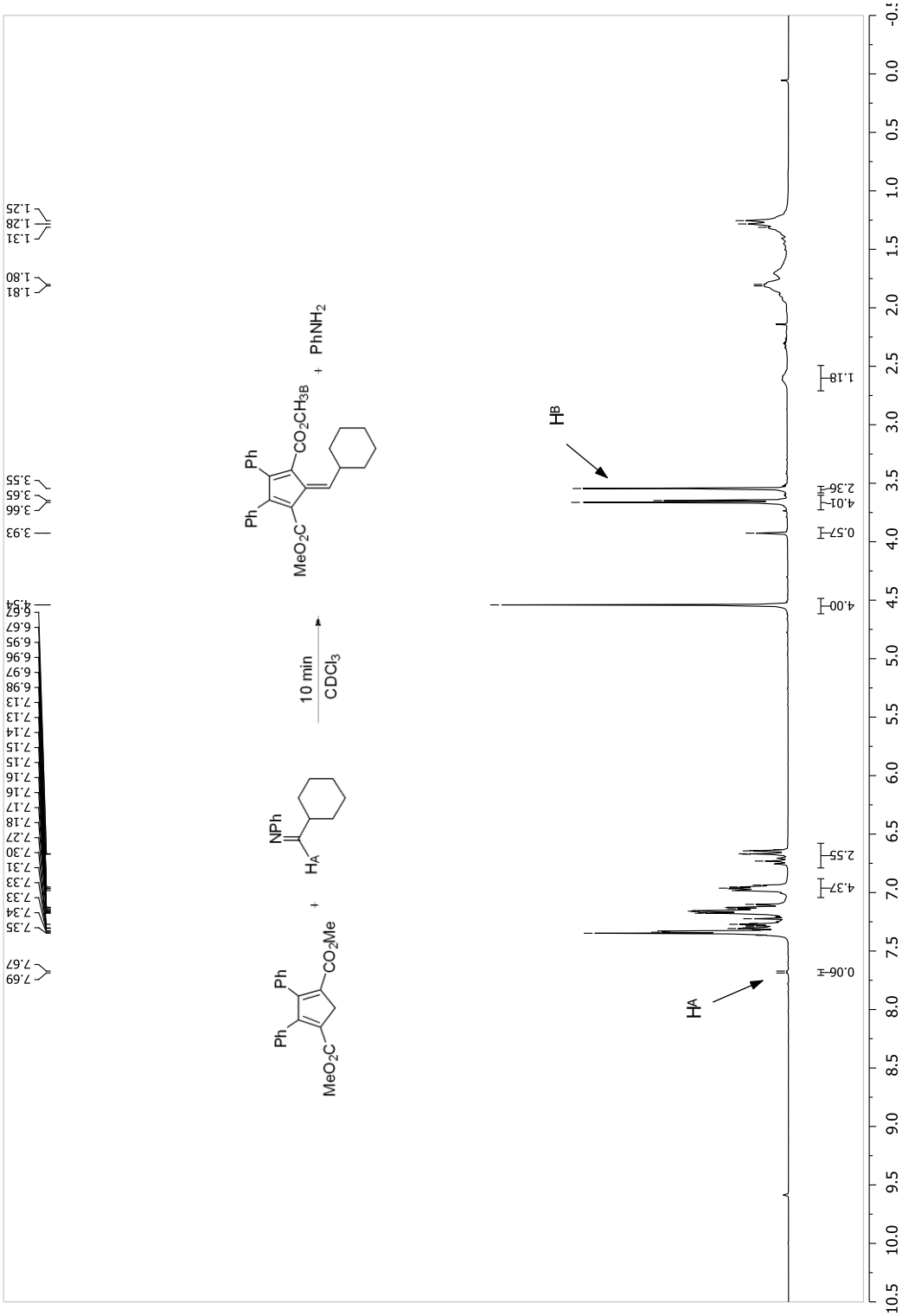

Ph
Ph
CO2Me
MeO2C
HB
NO2
+ PhNH2
2 hr
CDCl3
Ph
Ph
CO2Me
MeO2C
NPh
HA
NO2
+
HA
HB
f1 (ppm)

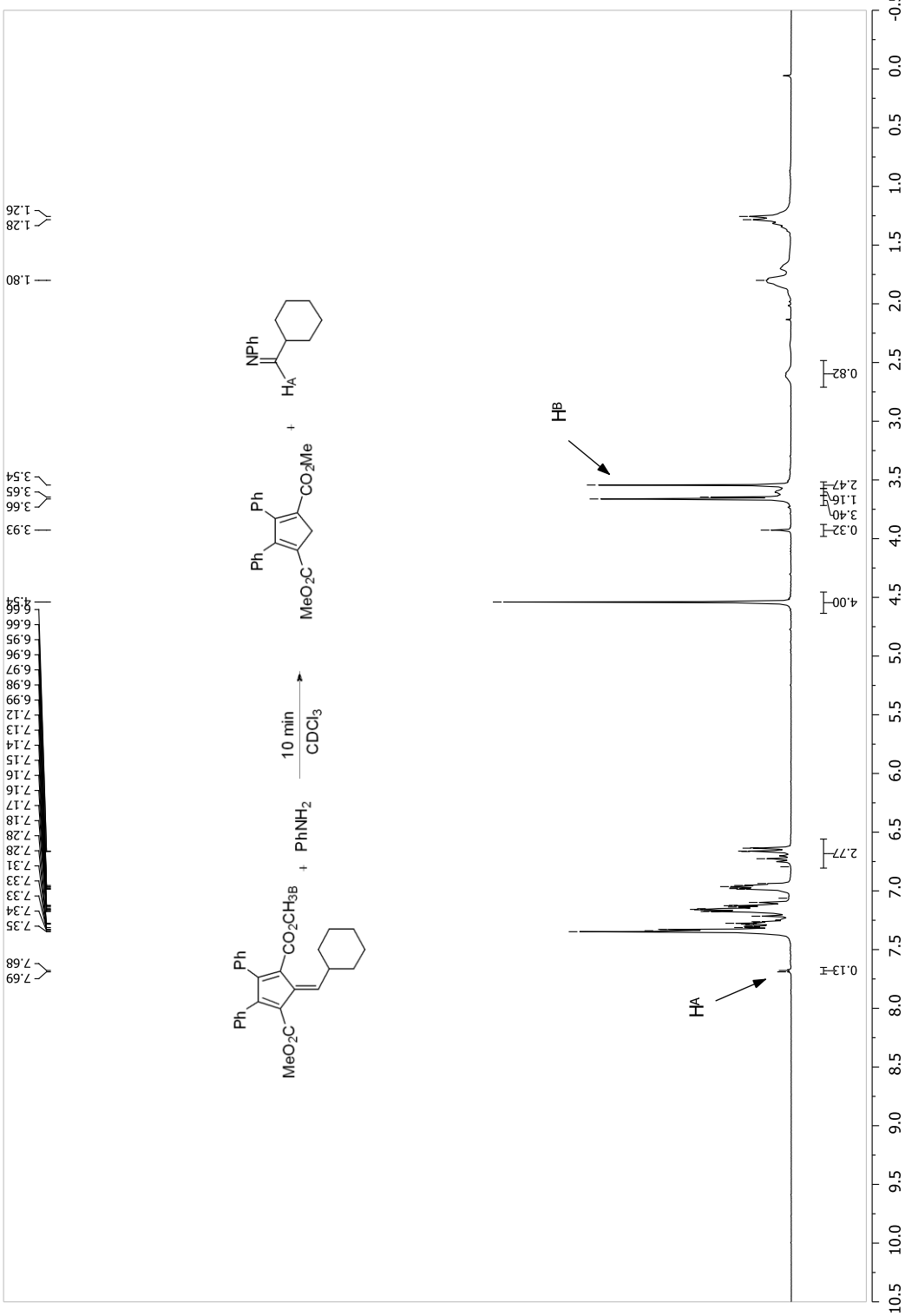

20 hr
CDCl3
PhNH2
Ph
CO2Me
MeO2C
OMe
NPh
HA
HB
HC
2.14
2.77
2.07
2.97
0.59
4.00
2.39
0.49
0.91

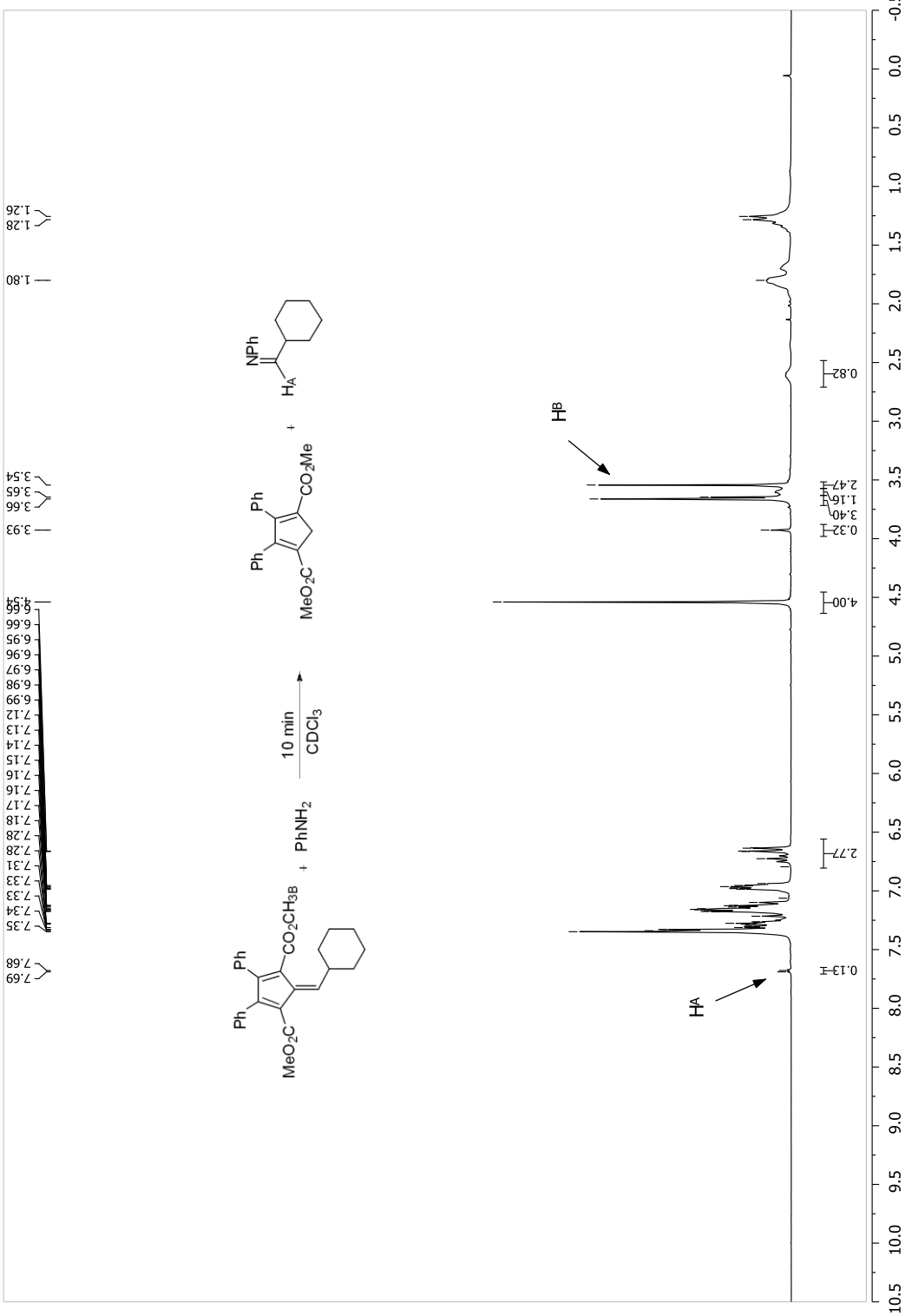

Ph
CO2Me
MeO2C
HC
OMe
+ PhNH2
20 hr
CDCl3
NPh HB
HA
HB
OMe
HB
HA + HC
8.39
8.36
7.84
7.81
7.46
7.43
7.35
7.34
7.33
7.30
7.28
7.21
7.19
7.18
7.17
7.16
7.16
7.15
7.15
7.13
7.12
7.10
7.06
6.99
6.98
6.94
6.91
6.66
6.63
3.84
3.83
3.81
3.65
3.59
3.11
2.02
1.26
1.23
1.21
0.87
0.55
1.50
2.31
4.00
0.51
2.97
1.58
2.43
1.95

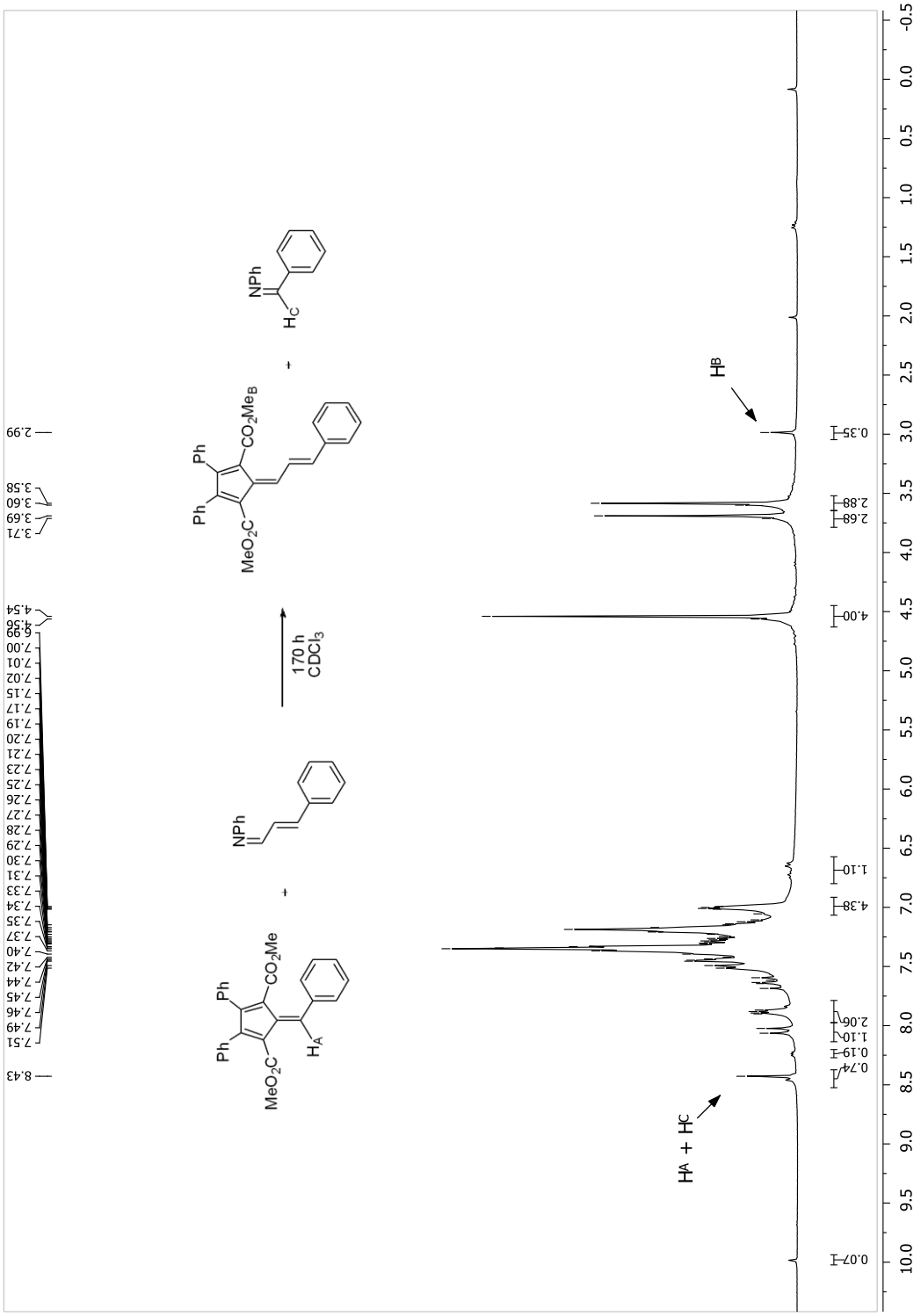

Ph
Ph
CO2Me
MeO2C
HB
+ PhNH2
12 hr
CDCl3
NPh
HA
+
Ph
Ph
CO2Me
MeO2C
HB
HA
0.04
0.87
1.00
1.92
4.02
2.58
4.00
2.89
0.46
3.69
8.25
8.23
8.05
8.01
7.49
7.49
7.37
7.35
7.34
7.33
7.30
7.28
7.26
7.19
7.18
7.17
7.15
7.14
7.12
7.10
7.01
7.00
6.99
6.98
6.98
6.97
6.66
6.63
6.63
3.69
3.65
3.58


Ph
Ph
CO2Me
MeO2C
HB
+ PhNH2
12 hr
CDCl3
NPh
HA
HB
HA
0.02
0.73
0.80
1.71
3.12
2.71
4.00
2.58
2.98
8.26
8.24
8.05
8.01
7.37
7.35
7.34
7.33
7.33
7.31
7.30
7.19
7.19
7.18
7.17
7.16
7.15
7.14
7.13
7.12
7.01
7.00
6.99
6.98
6.97
6.66
6.66
6.63
6.63
3.69
3.58


Ph
Ph
MeO2C
CO2Me
+
NPh
HA
10 min
CDCl3
Ph
Ph
MeO2C
CO2CH3B
+ PhNH2
HA
HB
0.06
4.37
2.55
4.00
0.57
4.01
2.36
1.18
7.69
7.67
7.35
7.34
7.33
7.33
7.31
7.30
7.27
7.18
7.17
7.16
7.16
7.15
7.15
7.14
7.13
7.13
6.98
6.97
6.96
6.95
6.67
6.62
3.93
3.66
3.65
3.55
1.81
1.80
1.31
1.28
1.25


Ph
Ph
CO2CH3B
MeO2C
+ PhNH2
10 min
CDCl3
Ph
Ph
CO2Me
MeO2C
+
NPh
HA
HA
HB
0.13
2.77
4.00
0.32
3.40
1.16
2.47
0.82
7.69
7.68
7.35
7.34
7.33
7.33
7.31
7.28
7.28
7.18
7.17
7.16
7.16
7.15
7.14
7.13
7.12
6.99
6.98
6.97
6.96
6.95
6.66
6.65
3.93
3.66
3.65
3.54
1.80
1.28
1.26


Ph
Ph
CO2CH3B
MeO2C
+ PhNH2
10 min
CDCl3
Ph
Ph
CO2Me
MeO2C
+
NPh
HA
HA
HB
0.13
2.77
4.00
0.32
3.40
1.16
2.47
0.82
7.69
7.68
7.35
7.34
7.33
7.33
7.31
7.28
7.28
7.18
7.17
7.16
7.16
7.15
7.14
7.13
7.12
6.99
6.98
6.97
6.96
6.95
6.66
6.65
3.93
3.66
3.65
3.54
1.80
1.28
1.26


Ph
Ph
CO2Me
MeO2C
HA
NPh
+
170 h
CDCl3
Ph
Ph
CO2MeB
MeO2C
NPh
HC
+
HA + HC
HB
8.43
7.51
7.49
7.46
7.45
7.44
7.42
7.40
7.37
7.35
7.34
7.33
7.31
7.30
7.29
7.28
7.27
7.26
7.25
7.23
7.21
7.20
7.19
7.17
7.15
7.02
7.01
7.00
6.99
4.56
4.54
3.71
3.69
3.60
3.58
2.99
0.07
0.74
0.19
1.10
2.06
4.38
1.10
4.00
2.68
2.88
0.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5